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ON THE ORIGIN OF MILIARY ANEURYSMS OF THE SUPERFICIAL CEREBRAL ARTERIES[1]

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I

In spite of the fact that there are to be found in the literature many careful studies of miliary aneurysms of the small arteries, especially those of the cerebral vessels, there still remains much doubt about the exact nature of these vascular peculiarities. The so frequent association of these cerebral aneurysms with repeated and finally fatal intracranial haemorrhage makes these aneurysms of the greatest importance and naturally serves as a stimulus, to any one who has had the opportunity afforded by good material, to attempt to learn something of their nature. This opportunity has come to us in the form of an unusually clear-cut and uncomplicated case where the aneurysms of the cerebral arteries were multiple and in which we have been able to do careful and quite satisfactory anatomical studies on both the aneurysms and the uninvolved cerebral vessels.

The information which was gained from this case, and from numerous others which we were able to find in the course of study of supposedly normal cerebral vessels, has led us into a general study of the problems presented by these aneurysms and their relation to the structure of the arteries of medium size. The results of these studies would seem to indicate that we have found a more rational explanation of the formation of the small multiple miliary aneurysms than is to be gained from a summation of current opinion.

One is in danger of considerable confusion in reading the various descriptions of small aneurysms which are so numerous in the literature. There seem to be many types of small aneurysms of the arteries of medium size, chief among which are those falling, generally speaking, into three groups, namely, (1) inflammatory, (2) traumatic

[1] Submitted for publication June 1, 1930.

and (3) congenital. For the sake of completeness may be mentioned three other groups or types (*a*) "Dehnungs-aneurysmen" (Busse (2), Emrich (3), (*b*) false or spurious aneurysms (Ellis (4), Pick (5)), and (*c*) arteriosclerotic aneurysms (Kerpola (22) *et al.*). That all these types, except those spoken of as congenital, exist is beyond question, although it is often difficult to be sure of the type to which some of the less characteristic and more incompletely described cases belong. As far as we can see, the best opinion is that the terms "congenital" and "multiple miliary" are synonomous, since it would appear that no one so far has found a satisfactory explanation of the multiple miliary aneurysms other than that they date from embryonic life and are, in fact, vascular malformations *per se*.

It is with the so-called "congenital" aneurysms that we are principally concerned in this study, a point which we should like to make clear from the beginning, in view of the fact that we shall also have something to say of the other types in our discussion of the mode of origin of the multiple miliary aneurysms. The scope of this work is also limited by the exclusion of all those aneurysms and related lesions of the vessels within the brain substance which were so carefully described by Charcot and Bouchard in 1866 (8) and termed "miliary aneurysms," and which have given rise to so much discussion of late in connection with intra-cerebral haemorrhage. We have made no study of the vessels within the brain substance, our observations being limited entirely to the superficial arteries of medium size at the base and in the sulci of the brain. The purpose of this study being essentially an enquiry into the nature and origin of miliary aneurysms, the scope of the work will be further limited by omission of details of clinical examinations, treatment, etc., only such facts being recorded as have some significant bearing upon the question of aetiology. The clinical aspects of the subject have been so adequately treated in the papers of Beadles (14), Lebert (15), Symmonds (16), Wallesch (17), John (18), Odquist (19), and others, that we experience no sense of incompleteness through their omission.

II

In the following case, a detailed record of which is given, a pecularity in structure of the wall of the cerebral vessels was found which sug-

gested a possible explanation of the origin of the multiple miliary aneurysms which were attached to these vessels.

Case 1. Autopsy No. H. 9952: Med. case, J. T., Male, Negro, aged 24. Died: 5 p.m., July 19, 1927. Autopsy: 10 a.m., July 23, 1927.

Anatomical diagnosis. Multiple small saccular aneurysms of superficial cerebral arteries (L. mid. cerebral and R. and L. anterior cerebral); rupture of aneurysm of R. anterior cerebral artery into subarachnoid space and into anterior horn of R. lateral ventricle, subarachnoid and intra-ventricular haemorrhage; cardiac hypertrophy and dilatation; pulmonary oedema; old inguinal scars; hypertrophy of femur bone-marrow.

Clinical history. The patient, a well developed negro man, aged 24 yrs., had been quite well before the day of his death, except for the occasional occurrence of headaches which were of no specific character. At two o'clock in the afternoon of the day of his death he was found on the floor in a semiconscious state. When the attending physician first saw the patient, the following physical findings were noted. The patient was stuporous; the head was drawn back and the neck quite rigid. The eyes were divergent, respirations were slow and of Cheyne-Stokes character. Babinski reflex positive. Three hours after the onset of the illness, a spinal puncture was done for the purpose of relieving intracranial pressure and bloody fluid was obtained. Respirations became progressively slower, and more difficult because of accumulation of mucus in the trachea. Death occurred three hours after the onset of the illness. The Wassermann test (blood) was negative. The urine contained a small amount of albumin and a few casts. The clinical diagnosis was subarachnoid haemorrhage with probable extension of haemorrhage into the ventricles.

Autopsy protocol. The *body* was that of a young negro man. It weighed 59 kgs. and measured 170 cm. in length. As one examined the external parts of the body no abnormalities of significance could be found. The various *body cavities* were in every way normal except for some discoloration which was obviously due to autolysis. The *heart* weighed 400 grams and measured as follows: tricuspid valve, 14 cm.; pulmonary valve, 7 cm.; mitral valve, 11 cm.; aortic valve, 7 cm.; left ventricle, 1.5 cm. thick; right ventricle, 5 mm. thick. The heart was therefore somewhat enlarged but it lacked the characteristics of a hypertensive heart in that the right side was more conspicuously enlarged than the left. The hypertrophy was so slight, however, that it was thought to be of little significance. There was said to have been some elevation of blood pressure at the time the patient entered the hospital, only a few hours before death, but one could see hardly enough in the heart to support the idea of chronic hypertension. The elevation of blood pressure must have been of temporary nature, and under the circumstances an observation none too reliable. In the lungs no lesions were seen, except the presence of some fluid. Macroscopic and microscopic examinations of all the other thoracic and abdominal viscera revealed no abnormality.

Brain and spinal cord. The spinal cord was normal. The brain showed no gross lesions except as directly related to the abnormalities in the superficial vessels. Numerous microscopic sections revealed no abnormality in structure except a small cyst-like cavity located deep in the white substance of the cortex. No inflammatory reaction was seen about this cavity and no softening of the surrounding tissue was apparent. Its exact nature was undetermined.

The vascular system was not unusual in general structure. In removing the circle of Willis and its various branches from the base of the brain, it was first necessary to peel away a thick sheath of blood which lay, in the subarachnoid space, over the entire surface of the pons and the adjacent structures. When all the blood was removed, five separate aneurysms were found whose relationships and characteristics were as follows:

Aneurysm No. 1 (Fig. 1). This aneurysm was found on the left anterior cerebral artery just at its point of origin, and in the oblique angle formed by the anterior cerebral and middle cerebral. The vessel from which the aneurysm arose showed a slight diffuse dilatation just proximal to the aneurysm so that it would appear that the aneurysm, which was distinctly saccular, might have been an exaggeration of this dilatation. Sections from the vessel wall at this point showed, however, a normal structure which was in great contrast to the structure of the wall of the aneurysm. The two features, the aneurysm and the dilatation, were therefore thought to be quite independent of each other. The greatest diameter of the aneurysm was 3 mm. and the smallest 2 mm. This lobulated sac was connected with the vessel by a thick pedicle, which was smaller than the greatest diameter of the aneurysm itself. When examined under the dissecting microscope, the outer surface of the aneurysm appeared smooth. No small vessels originated in the sac. The cavity of the aneurysm contained no blood-clot. The left anterior cerebral artery showed no further abnormality throughout its meningeal course. The presence of this aneurysm had caused no changes in the adjacent structures.

Aneurysm No. 2 (Fig. 1). This aneurysm was located exactly at the bifurcation of the left middle cerebral artery, 1.5 cm. from the point where this vessel left the circle of Willis. The aneurysm was saccular and lay in the acute angle formed by the division of the artery. The character of this bifurcation was somewhat peculiar since, as may be seen in the drawing, the two secondary branches left the mother vessel almost at right angles. The long axis of the cerebral artery prolonged, therefore, represented also the long diameter of the aneurysm. Under the dissecting microscope there appeared to be some slight diffuse dilatation of the three vessels just before they fused to form the fork. The aneurysm was not perfectly round. It had a lobulated surface as seen in aneurysm No. 1, and measured 5 mm. in maximum diameter. It was attached to the parent vessels by a pedicle which itself was irregular in shape and whose diameter was less than the smallest diameter of the aneurysm proper. The sac was empty. Its walls appeared, grossly, quite like the walls of the adjacent vessels except for an obvious variation in thickness in the different lobules. No small vessels were seen leaving

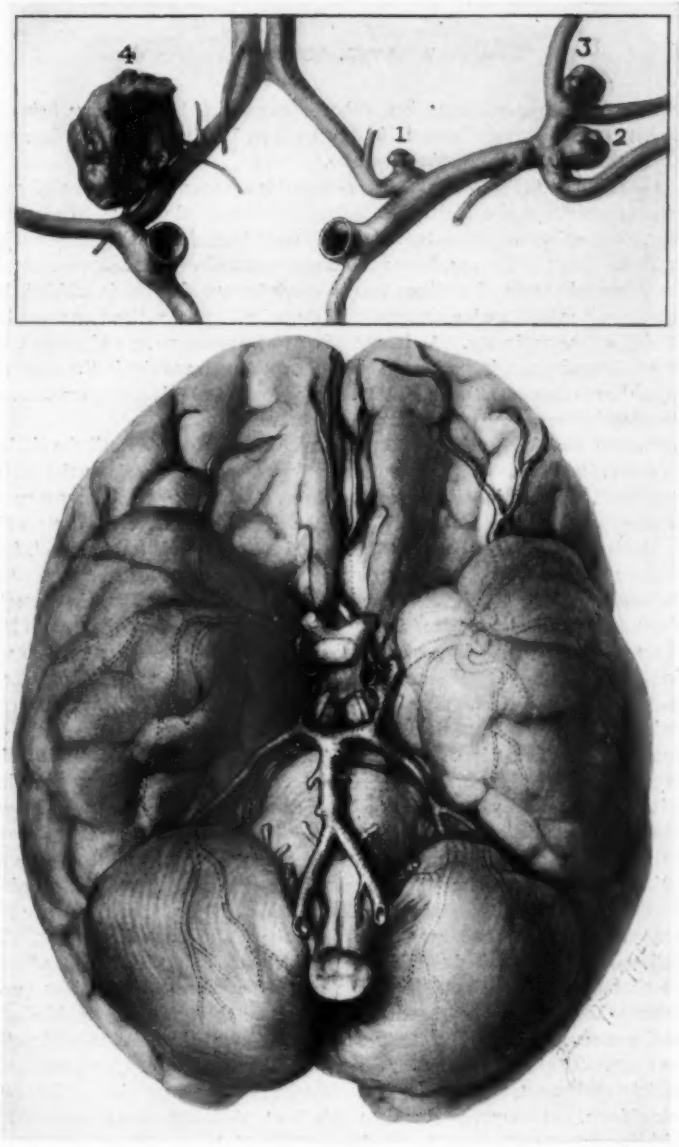

FIG. 1. CASE NO. H-9952. DRAWING OF THE BRAIN AND SUPERFICIAL VESSELS TO SHOW THE VARIOUS ANEURYSMS AND THEIR RELATION TO THE CEREBRAL VESSELS

Aneurysms Nos. 1, 2 and 3 were intact. Aneurysm No. 4 had ruptured

the aneurysm, its only connection with the circulating blood stream being its pedicle. This aneurysm lay free in the fissure of Rolando and produced no effects on the surrounding brain substance.

Aneurysm No. 3 (Fig. 1). The location of this aneurysm was the fork formed by the first division of one of the secondary branches of the left middle cerebral artery. Essentially its character was not different from that of the other two just described. The pedicle was, however, quite broad and so the sac appeared to be formed from the walls of all three vessels which formed the fork in which it lay. The surface was lobulated, each superficial elevation corresponding to a secondary widening of the main sac. As in the other two aneurysms, no blood-clot was present. In microscopic sections a small vessel was seen to arise in the aneurysm wall, although it was not seen grossly. The location of this aneurysm was such as to affect in no way the adjacent brain substance.

Aneurysm No. 4 (Fig. 1). This aneurysm could not be seen until the circle of Willis with its various branches had been completely removed from the surface of the brain, although it was considerably larger than any of the other aneurysms. The aneurysm arose from that portion of the right anterior cerebral artery which helps to form the circle of Willis. Its exact size was difficult to be sure of, for it was represented by a torn thick membrane to which was attached a mass of old thrombus and fresh blood-clot, the whole forming a mass 1.5 cm. in diameter. This mass was found embedded in the inferior surface of the right frontal lobe, and attached to the superior surface of the right anterior cerebral artery by a very thin pedicle. It was at once apparent, after removal of the mass from the brain substance, that this aneurysm had ruptured, for one could follow a direct communication between the bed of the thrombus and the anterior horn of the corresponding lateral ventricle. The ventricle was filled with fresh blood-clot and on subsequent section of the brain a large fresh tear was found in the septum lucidum, obviously produced by intra-ventricular haemorrhage. The aneurysm sac was recognized as a thickened, opaque, corrugated membrane lying over the greater part of the surface of the thrombus. A large rent in this membrane presented itself as the obvious source of the great haemorrhage. From the age of the thrombus (confirmed by microscopic examination), it was clear that there must have been previous small haemorrhages from the gradually weakening sac. Two small vessels were attached to the wall of this aneurysm but it was difficult to be sure that they had their origin in the sac. The microscopic sections (serial) distinctly show a connection between the sac and these vessels. A third small vessel was seen to leave the anterior cerebral artery at the point of origin of the aneurysm. The location of this aneurysm was such that it must have compressed the right optic tract, the right olfactory lobe and the right anterior portion of the optic chiasm. However, no symptoms relative to these structures were recorded, which fact may be accounted for by the small size of the aneurysm previous to the fatal rupture. One must remember in this connection, however, that little was known of the patient previous to the terminal haemorrhage.

Aneurysm No. 5. Aneurysm No. 5 was not seen in the gross examination of the vessels but was discovered in the course of microscopical studies, the results of which are recorded below. As seen in the serial sections, the aneurysm occupied the same relative position as the other aneurysms already described, that is, the fork produced by a dividing vessel. Again one saw the irregular lobulated surface and, as in the other aneurysms, no thrombus was present in the sac. Further description of this aneurysm is to be found below.

Microscopic study of aneurysms. All five aneurysms described above were fixed in formalin and sectioned serially. The block in each case was so cut as to show the relation of the aneurysm to the three vessels forming the fork in which the aneurysm lay. Before fixation, a solution of gelatin was injected into the whole vascular system at the base of the brain, in order to secure fixation of the vessels and aneurysms in their distended state. The microscopic structure of the various aneurysms was found to be quite the same except in the case of Aneurysm No. 4, where rupture occurred. A composite description of Aneurysms 1, 2, 3 and 5 will be made in view of their structural similarity. However, it is desirable in the case of Aneurysm No. 4 to give a separate description, since one finds peculiarities in structure in its walls which are important in connection with the process of rupture.

The walls of Aneurysms No. 1, 2, 3 and 5 (Fig. 2) were intact, and, as before mentioned, unobscured by thrombus or fresh blood-clot. The portion of the vessel wall from which the sac arose showed no abnormality. The intima, internal elastic membrane, muscularis and adventitia were quite unaltered. Exactly at the point where the sac began, the intima was tremendously thickened. The entire inner surface of the sac was formed by this thickened fibrous intimal tissue. The thickness varied much from place to place and indeed was in some areas hardly more than that of the normal intimal sheath in the cerebral arteries of larger size. There were many cells lying in this proliferated intima but the bulk of the tissue was formed by intercellular substance which was identified as collagen. The cells were not unlike ordinary fibroblasts. There were no wandering cells present nor did one see any other indication that there had been at any time, at this site, an inflammatory process. The internal elastic membrane disappeared rather abruptly at the border of the sac and did not appear anywhere in the wall of the aneurysm. The ends of this membrane were rather blunt, and not frayed out as customarily seen in arteriosclerosis. The muscular coat likewise disappeared at the beginning of the sac. The end of this layer was in some instances quite sharp but there was occasionally seen a gradual thinning out of the muscle cells with finally complete disappearance of this layer. From that point on throughout the wall of the aneurysm no muscle was to be seen. The thickness of the adventitia varied somewhat. In places it was thicker and of a more hyaline character than that of the adjacent normal vessel wall, while in other locations it was not different from the normal. Elastic-tissue fibres were not present in abnormal number. A few round cells, lymphocytes or plasma cells could be seen, but their

FIG. 2. CASE NO. H-9952. MICROPHOTOGRAPH OF FULL SECTION OF ANEURYSM NO. 3, SHOWING ITS RELATION TO THE ADJACENT VESSELS

The aneurysm lies in the angle formed by the two major branches of a primary branch of the left middle cerebral artery.

presence was by no means constant. Nothing was seen to indicate any definite progressive inflammatory process in the aneurysm wall or in the tissues of the adjacent vessels.

In Aneurysm No. 4 the essential findings in microscopic studies were the same.

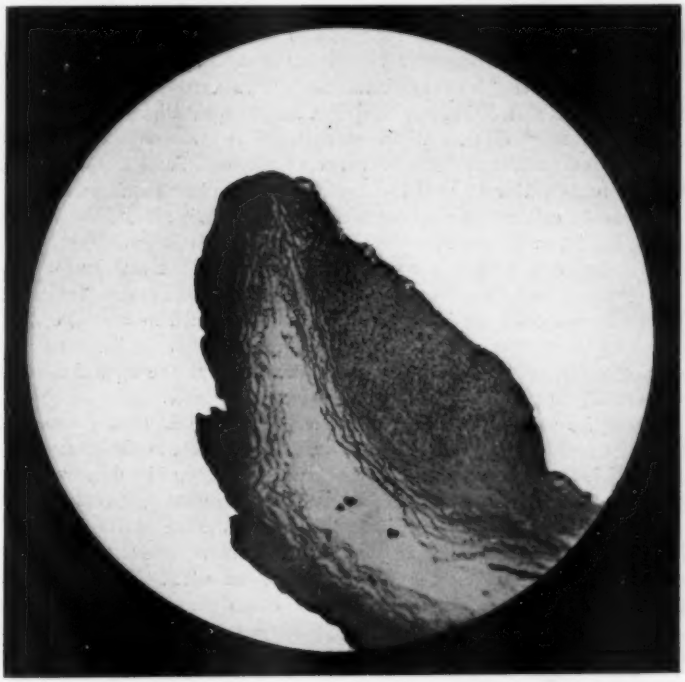

FIG. 3. CASE NO. H-9952. MEDIUM-POWER MICROPHOTOGRAPH OF ONE OF THE MARGINS OF ANEURYSM NO. 3, THE LOW POWER OF WHICH IS SEEN IN FIG. 2

The main features of interest are the total absence of the muscular coat in the aneurysm wall, the cessation of the internal elastic membrane at the margin of the aneurysm, the normal adventitia and the thick fibrous intimal plaques which form the greater part of the aneurysm wall. The internal elastic lamella appears as a thick black band and should be distinguished from the delicate black membrane which lies on the surface of the intimal plaque toward the lumen. This membrane represents a thin coat of gelatin injected into the vessels to maintain the natural form of the aneurysms.

as those in Aneurysms No. 1, 2, 3 and 5. The absence of muscle and elastic tissue, with their more or less abrupt disappearance at the edge of the sac, was conspicuous. But the character of the sac differed from that in the other aneurysms in that its wall showed no definite intimal plaques but on the contrary its whole thickness was formed by hyaline connective tissue, which showed more or less continuity with the thrombus which lay next to it. The picture was obviously that arising from hyalinization of pre-existing tissue and organization of adjacent thrombus. There were present several laminae of this hyalinized tissue. In following the serial sections through the whole mass representing the aneurysm, with its adherent clot, it became clear that several breaks had occurred in the laminated wall which subsequently became plugged by organized thrombus. The most recent tear and that which led to the terminal haemorrhage was found to be a tangential break with outflow of blood between the laminae forming the sac wall and eventually exit into the subarachnoid space through a break in the outer layers at a point quite removed from the rent in the inner layers. This terminal rupture occurred in a place almost exactly opposite to the attachment of the aneurysm to the parent vessel and in a place which must have been either in direct contact with the overlying inferior surface of the frontal lobe cortex, or, more likely, completely embedded in the substance of the brain. It is, therefore, no wonder that the out-flowing blood bored its way through the cortical substance and eventually into the anterior horn of the lateral ventricle.

Microscopic study of arteries other than those connected with the aneurysms. In view of the constant location of the aneurysms in this case at the bifurcation of vessels and, indeed, characteristically in the acute angle formed by the parent vessel and its two branches, it was thought worth while to study numerous arteries in the cerebral system with special regard for their structural character at points of bifurcation, and so more than twenty different blocks were selected, each representing a different vessel or different parts of the same vessel. Not only points of bifurcation were chosen but longitudinal and cross-sections were made from various vessels at places quite removed from points of division. The arteries that were studied were seven in number as follows: (1) right middle cerebral, (2) left middle cerebral, (3) anterior cerebral, (4) vertebral, (5) basilar, (6) posterior cerebral, (7 posterior communicans. From this case no vessels outside the cranial cavity were studied.

The essential findings derived from the above studies may be noted as follows. In almost every section taken from the block showing dividing points of the two middle cerebral arteries, a peculiar defect in the muscularis was found exactly at the apex of the acute angle formed by the division of the vessel. This defect is illustrated in Fig. 4 which is a photograph of vessel walls taken from the case under discussion. Perhaps a better illustration of this defect is to be seen in Fig. 5, a photograph of a vessel from a case chosen at random from a group of autopsies for the purpose of control studies. The place of the media is taken by connective tissue which is not distinguishable from that which forms the adventitia of the

artery, and is continuous with this layer. The defect may be quite small, being represented by a sheath of connective tissue extending through the muscular layer from the internal elastic membrane at the apex of the angle to the adventitia. In

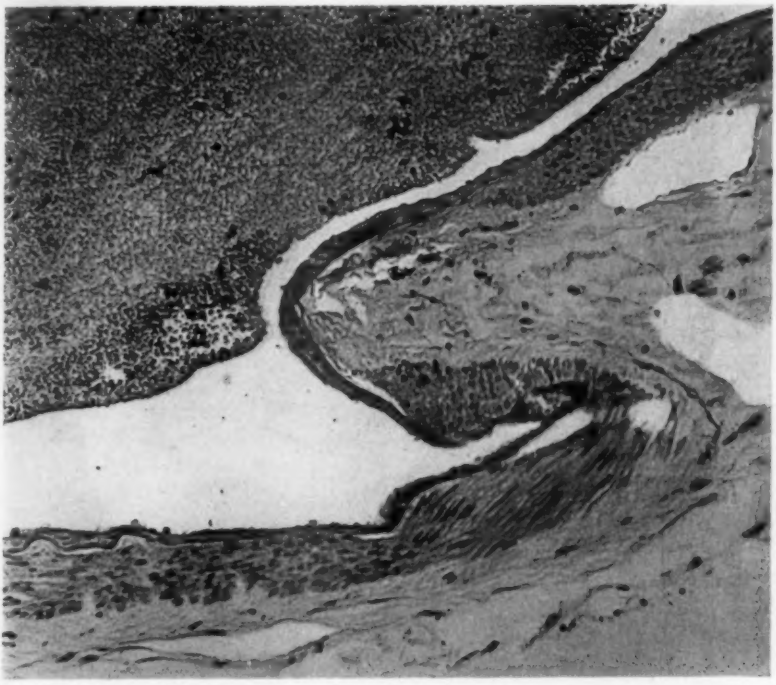

FIG. 4. CASE NO. H-9952. HIGH-POWER MICROPHOTOGRAPH OF A CHARACTERISTIC MEDIAL DEFECT LOCATED IN THE ACUTE ANGLE FORMED BY THE BRANCHES OF A CEREBRAL VESSEL TAKEN FROM THE ANEURYSM CASE SHOWN IN FIG. 1.

In the total absence of muscle the vessel wall at this point is composed of adventitia, internal elastic membrane and intima, all of which are normal. The photograph is of one of a series of sections, all of which showed the same relationship.

other cases a considerable gap is seen in the muscularis as represented in Fig. 5. Associated with this defect one sees no inflammatory reaction and no necrosis of tissue. The connective tissue replacing the muscle, furthermore, has none of the

characteristics of a scar but on the contrary appears in every way like a simple continuation of the over-lying adventitia. In the obtuse angle formed by the dividing vessel were to be seen somewhat similar medial changes but such a location was of rarest occurrence. When the defect was seen in this unusual position it

FIG. 5. CASE NO. H-10183. LOW-POWER MICROPHOTOGRAPH OF A MEDIAL DEFECT IN THE WALL OF A VESSEL TAKEN FROM A CASE WITH NO INTRACRANIAL LESION

The vessel shown is one of the middle cerebral arteries and the location that of the origin of the primary branch of the vessel. The location and general character of the imperfect media is typical.

was, as a rule, not complete, irregular arrangement of the muscle cells and great thinning out of this layer composing the abnormality. Here, as in the acute angle, nothing whatever indicating an inflammatory process either past or present

could be made out. In other sections of these vessels taken from places removed from points of division, nothing abnormal could be found.

The structural findings in the other arteries studied included none of the peculiarities found in the middle cerebrals. This is perhaps accounted for by the fact that the dividing points were not especially selected in choosing the blocks from these arteries. The blocks represented principally longitudinal and cross-sections from the intervals between branches. The findings in this group of sections therefore would seem to indicate that the muscularis peculiarity is limited to the immediate zone in which the division of the vessel occurs.

One may summarize the observations in the case as follows:

1. The aneurysms were multiple but arose only from vessels belonging to the carotid system.
2. The aneurysms were all located at points of bifurcation of the vessels.
3. There was a total absence of evidences of acute or chronic inflammation in connection with the aneurysms.
4. A definite defect in the muscularis was found at numerous points of division in the right and left middle cerebral arteries.
5. No clear-cut muscularis abnormality was found at points other than those of bifurcation in the middle cerebrals, nor in numerous other arteries.
6. The muscularis defect was never found associated with recognisable inflammatory or degenerative changes in the vessel wall.
7. The location of the aneurysms corresponded exactly to the location of the muscularis defect.

In the course of examination of the arteries from the brains of some seventy cases which were taken at random from our autopsy material for the purpose of determining how frequently the medial defect just described occurs in supposedly normal individuals, a group of twelve cases was found in which aneurysms of the cerebral arteries were present. Since all except four of these aneurysms were identical with those described in the case above, only a brief summary of the cases is given here in the form of a tabulation. Where any special features occurred, as was the case in the four exceptional cases just mentioned and in one of the group of eight remaining, characteristic miliary aneurysms, a special description of the aneurysm will be given later in our discussion of the mode of formation of these aneurysms.

In Table II are to be found summarized an additional group of cases which were chosen at random from routine autopsies with the idea of determining how frequently the medial defect could be found in cases in which no aneurysms were known to exist. Since it was thought desirable to learn of any possible association of the muscle defect with recognizable disease processes, there were included in this group of control cases a certain number of meningeal infections and other disease processes as follows:

Tuberculous meningitis	1
Syphilitic meningitis and arteritis	1

TABLE I

Cases in which aneurysms were found in the course of examination of 70 cases chosen at random for determination of presence of medial defects at bifurcations of cerebral arteries

CASE NUMBER	AUTOPSY NUMBER	SERVICE NUMBER	AGE SEX RACE	ANATOMICAL DIAGNOSIS	CLINICAL FINDINGS	SIZE AND LOCATION OF ANEURYSM	PRESENCE OF MEDIAL DEFECT
2	H-10333	H.L.H. 45677	8 M–W	Ruptured aneurysm of posterior cerebral artery; subarachnoid and intraventricular haemorrhage	Sudden unconsciousness followed by stupor for 2 days. Headache; stiff neck; lateral nystagmus; positive Kernig's sign; retinal haemorrhages; bloody spinal fluid; death with general convulsions	2.5 cm. Posterior cerebral	+
3	H-10424	Med. 59928	32 M–W	Bilateral aneurysm of middle cerebral arteries at their origin from the carotids; rupture of aneurysm of left middle cerebral with formation of false aneurysm producing pressure on third nerve; subarachnoid haemorrhage; fresh infarct of left cerebrum	Pain below and behind eyes; ptosis of left eye-lid and dilatation of left pupil; loss of accommodation. Wassermann reaction negative; B.P. 120/78; P. 60, R. 8; bloody spinal fluid just before death	Both middle cerebrals at origin from carotid. A third microscopic aneurysm at point of exit of small branch from left middle cerebral	+
4	H-10573		28 F–W	Ruptured aneurysm of right middle cerebral artery; subarachnoid haemorrhage; retinal haemorrhages; atrophy and necrosis of part of right temporal lobe due to pressure from aneurysm	Sudden unconsciousness 37 days before death. Severe pain in right side of head; blurred vision; rigidity; convulsions, vomiting, involuntary urination just before death. B. P. 140/98. T. 97.6; bloody spinal fluid; negative Wassermann	8 mm. Point of primary bifurcation of right middle cerebral	+

5	H-10668	Med. 60697	33 M–C	Cardiac hypertrophy, arteriosclerosis, myocardial scars; chronic nephritis; fibrinous pericarditis; abscess in right tonsil; lobular pneumonia; fibrinopurulent pleurisy; microscopic aneurysm of middle cerebral artery	Clinical signs and symptoms characteristic of cardiovascular renal disease. B. P. 220/112	Earliest stage of formation; microscopic. Primary branching point of left middle cerebral	+
6	H-10793	Med. 68426	50 F–C	Acute tonsillitis, laryngitis, pharyngitis and tracheitis; lobular pneumonia; streptococcus septicaemia; acute splenic tumor; miliary aneurysm of middle cerebral artery; Dehnungs-aneurysma of left anterior cerebral artery; anomalous origin of right anterior cerebral artery; obesity	T. 103, P. 116, R. 32, B.P. 160/100. Blood culture positive for beta hemolytic streptococcus. Wassermann negative	"Dehnungs-aneurysma" on anterior communicans. Miliary microscopic aneurysm on middle cerebral at point of primary division	+
7	B.V. 3737	Med.	33 M–C	Ruptured miliary aneurysm of right anterior cerebral artery; subarachnoid, intracerebral and intra-ventricular haemorrhage. Arteriosclerosis; hypertrophy and dilatation of heart; chronic passive congestion of viscera	Sudden unconsciousness preceded by headaches. Convulsions following a second attack of unconsciousness. B.P. 230/95, T. 101, P. 120, R. 48. Spinal fluid bloody. NPN 42. Continued coma and convulsions until death	8 mm. Right anterior cerebral	+
8	B.V. 3816	Med.	48 F–C	Arteriosclerosis; chronic arteriolosclerotic nephritis; cardiac hypertrophy and dilatation. Intra-cerebral and intra-ventricular haemorrhage; small arteriosclerotic aneurysm of left carotid at base of brain; lobular pneumonia; myomata of uterus; cholelithiasis	Coma, history of cardiovascular disease with nephritis. B.P. 234/114. Wassermann negative. Blood in spinal fluid	5 mm. Attached to carotid artery but not at point of bifurcation. Microscopically not a miliary aneurysm but an arteriosclerotic aneurysm	+

TABLE I—*Concluded*

CASE NUMBER	AUTOPSY NUMBER	SERVICE NUMBER	AGE SEX RACE	ANATOMICAL DIAGNOSIS	CLINICAL FINDINGS	SIZE AND LOCATION OF ANEURYSM	PRESENCE OF MEDIAL DEFECT
9	B.V. X-2	Med.		Not available	Not available	Microscopic at point of bifurcation of middle cerebral	+
10	-10107	Gen. No. 207817	39 M–W	Chronic nephritis; cardiac hypertrophy and dilatation; anasarca; arteriosclerosis; miliary aneurysm of right middle cerebral artery	Symptoms and signs characteristic of cardio-vascular renal disease. B.P. 231/160; myocardial failure; uraemic coma. Wassermann negative.	Microscopic. Right middle cerebral at point of division	+
11	H-10183		58 F–C	Cardiac hypertrophy and dilatation; old subarachnoid cerebellar haemorrhage. Chronic nephritis; arteriosclerosis. Huge myomata of uterus causing compression of abdominal and thoracic viscera	Signs and symptoms of myocardial insufficiency. B.P. elevated. Death from myocardial failure due to compression and displacement of thoracic viscera caused by huge myomatous uterus	Microscopic aneurysm at point of division of middle cerebral	+
12	H-10750		65 M–W	Emphysema; cardiac hypertrophy and dilatation; chronic passive congestion of viscera; bilateral hydrothorax; pronounced generalized arteriosclerosis with extreme changes in cerebral arteries; dissecting arteriosclerotic aneurysm of left vertebral artery; chronic cholecystitis and cholelithiasis; moderate prostatic hypertrophy	Hallucinations; delirium; states of excitement and destructive tendencies; Wassermann negative	1 cm. in diameter. Left vertebral artery, not associated with exit of branch	+
13	M-R-1		Adult young	No lesions found at autopsy	Executed criminal	Microscopic "Dehnungs-aneurysma" at bifurcation of right middle cerebral	+

TABLE II

Cases chosen at random from autopsies in which no multiple miliary aneurysms were known to exist and studied with purpose of determining the presence of medial defects in vessels at different locations and the relation of the presence of the medial defect to age

PATHOLOGICAL NUMBER	PRINCIPLE PATHOLOGICAL FINDINGS	AGE	MEDIAL DEFECT		
			Brain	Heart	Mesentery
H-9620	Syphilitic meningitis; gummata of cerebral arteries; rupture of gummatous artery with fatal subarachnoid haemorrhage	28	+		
H-10124	Streptococcus viridans endocarditis; multiple brain abscesses; ruptured mycotic aneurysm of basilar artery; meningitis	8	+		
H-10117	Pneumococcus meningitis	6 months	+		
H-10090	Collapse following hysterectomy. No anatomical lesions found at autopsy	47	+		
H-10151	Exophthalmic goitre; cardiac hypertrophy; Moderate arteriosclerosis; cirrhosis of liver	49	+		
H-10150	Carcinoma of breast with extensive metastases	38	+		
H-10190	Meningococcus meningitis; small subarachnoid hemorrhage at base of brain, source undetermined	6 months	+		
H-10131	Ulcerative tonsillitis with secondary phlegmonous inflammation of cervical tissues; erysipelas; pneumonia; acute interstitial nephritis	10 months	0		
H-10157	Clinical history of postpartum eclampsia; focal necroses in liver; atrophy and scarring of right kidney; hypertrophy of left kidney; aspiration pneumonia	34	+		
H-10178	Lobular pneumonia; multiple lung abscesses; fibrinopurulent pleurisy; rickets	6 months	+		
H-10185	Generalized tuberculosis; tuberculous meningitis	4½ months	+		
H-10125	Diphtheritic colitis; lobular pneumonia; fibrinopurulent pleurisy	6 months	+		
H-10195	Interstitial bronchopneumonia; lung abscess; empyema; fibrinous pericarditis	5 months	0		
H-10096	Acute myeloid leukaemia with multiple haemorrhages; no intra-cranial lesion	Adult	+		
H-10085	Subacute nephritis; myocardial hypertrophy; lobular pneumonia; chronic salpingitis and oöphoritis	32	+		
H-10080	Chronic pyelonephritis associated with aplasia of one kidney; retinitis with detachment of retina; thrush; diphtheritic colitis; lobular pneumonia	8	+		

TABLE II—*Concluded*

PATHOLOGICAL NUMBER	PRINCIPLE PATHOLOGICAL FINDINGS	AGE	MEDIAL DEFECT		
			Brain	Heart	Mesentery
H-10063	Clinical history of acute gastro-intestinal indigestion; no lesions found	4 months	0		
H-10697	Subdural haemorrhage from birth trauma	Stillborn	0		
H-10698	Generalized jaundice; petechial haemorrhages in stomach mucosa; superficial ulcers of stomach mucosa; haemorrhage into stomach, and muscles of thigh; lobular pneumonia; septicaemia; intra-cranial haemorrhage at base of brain	4 days	+		
H-10708	Patent ductus arteriosus and foramen ovale; atelectasis of lungs; intra-cranial haemorrhage due to birth trauma	Stillborn	+		
H-10711	Prematurity; intra-cranial haemorrhage due to birth trauma	5 days	0		
M-R-2	Executed criminal—guillotined. No lesions found in brain	Adult	+		
M-R-3	Executed criminal—guillotined. No lesions found	Adult	0		
M-566	Mitral and aortic endocarditis; fibrinous pericarditis; pulmonary tuberculosis; lobular pneumonia; arteriosclerosis	68	+	0	
M-567	Erysipelas; otitis media; coronary and aortic sclerosis	61			+
M-568	Carcinoma of stomach with metastases; atrophy of heart and liver; anasarca; decubitus ulcers	49	+	0	0
M-573	Pulmonary tuberculosis	47	+	0	0
M-586	Purulent meningitis; bronchopneumonia; pulmonary tuberculosis	Adult	0	0	0
M-574	Hypertrophy and dilatation of heart; bronchopneumonia; chronic cholecystitis; multiple polyps of colon	78	+	+	+
M-581	Hypertrophy and dilatation of heart; coronary sclerosis; bronchopneumonia	64	+	0	0
M-607	Erysipelas; bronchopneumonia; otitis media; generalized arteriosclerosis	57	0	0	0
M-622	Generalized tuberculosis	23	+	0	0
M-608	Old cerebral haemorrhage; arteriosclerosis; chronic nephritis; pachymeningitis haemorrhagica interna	61	+	+	0

Note: A blank space in the column for recording presence or absence of medial defects signifies that no examination was made of the corresponding vessels. The positive or negative results in this table are results obtained from examination of numerous sections from different vessels.

Meningococcus meningitis	1
Pneumococcus meningitis	2
Haemorrhage due to cerebral birth trauma	4
Old cerebral haemorrhage	2
Ruptured mycotic aneurysm with meningitis	1

The material was derived from patients of all ages, including stillborn children. In the greater number of cases only arteries of the brain were examined. In a group of ten cases vessels from brain, mesentery and coronary arteries were examined.

In the table there appear facts which may be summarized as follows:

(1) Twenty-five of thirty-three cases showed a medial defect at the bifurcation of the vessels studied, similar to that seen in Aneurysm Case No. 9952.

(2) Of nine cases in which coronary vessels were studied, two showed defects at points of origin of the branches of the coronary arteries. Defects were at the same time found in the cerebral and mesenteric arteries in one of these cases and in the cerebral and not in the mesenteric vessels in the other case.

(3) Of nine cases in which the mesenteric arteries were examined, two showed medial defects at points of division. In one of these cases no examination was made of the coronary and cerebral vessels. In the other case medial defects were found in both coronary and cerebral vessels.

(4) Whenever defects in the musculature occurred in the mesenteric or coronary arteries they were usually, but not always, present in the cerebral vessels, while the reverse was not at all true. The cerebral muscularis defect was present in numerous cases in which the vessels of the heart and mesentery were normal.

(5) The muscularis defect was present in children as well as in adults, and indeed of practically equal frequency. Nine of fourteen children, all of whom were eight years of age or under, and fourteen of nineteen adults showed the defect. Of the two stillborn children examined, one showed the muscularis defect. Two of four children, five days of age or younger, showed the defect.

(6) There was no demonstrable relationship between the presence of an acute inflammatory reaction in the meninges surrounding the vessels and the observed muscularis defect. All six cases with inflammatory meningeal lesions showed this abnormality but at the same time a far larger number of cases without any intracranial inflammatory disease were also positive.

That one should be cautious and conservative in drawing conclusions from this series of cases need not be emphasized. The number of cases is far too small. The deductions which have been made from the study have, however, a strikingly suggestive value, since the facts indicate clearly that the muscularis defect occurs frequently in cases unassociated with aneurysms or cerebral and vascular disease, as well as with aneurysms as has been seen in Table I.

III

The essential problem presented by the findings as given in Section II may be adequately stated in the form of a question. What is the nature of the peculiar specific muscularis defect as found so frequently in the angle formed by the bifurcation of the various arteries, and what part, if any, does it play in the origin of aneurysms at this point?

The microscopic character of the muscularis defect is such as to leave no doubt that it is not a lesion belonging to any specific inflammatory process. The picture is always such as to indicate that no muscle was ever present at the site of the defect, or that the muscularis in its development was laid down as a very irregularly formed layer of muscle with intervening gaps filled by connective tissue. In many sections in which no complete absence of muscle was found it was frequently noted that great irregularity of arrangement and distribution of muscle cells existed. In the control studies were purposely included cases with active acute and chronic inflammatory processes in the meninges and in the arterial walls themselves. In purulent meningitis one may see extensive changes in the adventitia of meningeal vessels and often an inflammatory exudate may be seen in the sub-endothelial layers. Necrosis in the muscular layer sometimes occurs. These changes, however, are clear-cut and in active progress, allowing no doubt as to their character. Furthermore, they are found everywhere in the course of the vessel and not confined to the point of bifurcation. For these reasons it is hardly conceivable that the medial defect can have a previous acute inflammatory arteritis as its basis. In the case of chronic inflammatory lesions in the cerebral arteries, as illustrated by the case of syphilitic meningitis and arteritis and that of tuberculous meningitis, the lesions are again as a rule diffuse, but when localized they are so specific as to leave no doubt as to their character. That our muscularis defect could be the result of such a process seems as unlikely as that it should arise from an acute inflammatory reaction in the arterial walls. Since the defect, as always seen in our cases, is quite clearly unassociated with any active process, one must consider the possibility of its being a scar resulting from the healing of a previous inflammatory focus. It is difficult to believe, however, that such a lesion as a miliary gumma or other similar condition, even though

healed, could ever produce so little damage to the arterial wall and at the same time be so specifically localized as is the case with the muscularis defect.

Just as one feels safe in saying that the muscularis defect has no connection with inflammation in the vessel walls, it is possible to be reasonably certain that the lesion is in no way dependent upon degenerative changes resulting from intoxications in the course of acute infections. Focal degenerations in the muscular system are thought by some to be due to toxic substances (Henke-Lubarsch (7)), but such degenerations are diffusely scattered, involving no specific segment and may affect any or all layers of the vessel walls but perhaps most characteristically the intima and the elastica. It is far from believable that such focal necroses could lead to our muscularis defect which is so specifically localized.

If one recalls for a moment's consideration the essential features of arteriosclerosis, it becomes at once apparent that the defective muscular coat at points of bifurcation can have no connection with this disease. In the course of this study the defect has been seen quite as often in cases where no sclerosis of the vessels existed as in cases where the process was extreme. One need only refer to Figures 4 and 5, photographs of medial defects unassociated with any changes in the intima, to feel satisfied as to the total independence of the two processes. That the media may be completely destroyed in the development of a sclerotic lesion is known to everyone, but such changes without definite intimal involvement have not been recorded.

With the exception of the three pathological processes which have just been discussed, that is, inflammation *per se*, degeneration from some cause associated with infectious processes, and arteriosclerosis, there are no recognized lesions of blood vessels, as far as we know, which might account for the muscularis defect. There remains then only the possibility of malformation of the vessel wall. That this muscularis defect is a developmental imperfection in the arterial wall seems to be definitely proven by its demonstration in a stillborn child (Case No. H-10708, Table II).

Having thus been able to demonstrate satisfactorily that the muscularis defect dates from embryonic life, it seemed to us worth while to attempt to find out its mode of development. For this purpose we have

TABLE III

Summary of observations made on the state of development of the media of the aorta and its immediate branches in human embryos of different ages

EMBRYO NUMBER	EMBRYO LENGTH	SERIAL SECTION NUMBER	STATE OF DEVELOPMENT OF AORTA	STATE OF DEVELOPMENT OF OTHER ARTERIES
	mm.			
1836	11	18*	About endothelial tube representing aorta appear undifferentiated mesenchymal cells. No recognizable muscle	All branches of aorta represented by simple endothelial channels without any surrounding mesenchymal alteration
695	13.5	38	No recognizable muscle in aortic wall. Concentration of mesenchymal cells about endothelial aorta more pronounced	All branches of aorta represented by simple endothelial channels
940	14	25	No muscularis as such recognizable. Mesenchymal cells more differentiated than in No. 1836 and No. 695	No recognizable muscularis in mesenteric and intercostal arteries
719	15	10	Muscle coat fairly well developed in gross form, being represented by a thick layer of mesenchymal cells having circular arrangement	No muscularis seen in any of the aortic branches
74	16	24	Aortic wall much the same as in embryo No. 719	No signs of development of muscle about the branches of the aorta
409	18	21	Aortic wall composed of delicate endothelial tube surrounded by a sheath of cells quite well differentiated from the adjacent undifferentiated mesenchymal cells. Cells in this sheath arranged in a regular circular way	Intercostal arteries still represented by simple endothelial tubes which course through the fairly well differentiated muscularis of the aorta
4570	30.7		Aortic wall now recognizable as muscular structure although the muscle cells still resemble somewhat the less differentiated mesenchyme in the neighboring tissue	Carotid arteries show marked differentiation in the mesenchymal cells lying immediately about the endothelial channels
3669	34†	34	Aortic wall essentially as in embryo No. 4570	Intercostal arteries show no medial differentiation whatever
4455	78.5	70	Aortic wall shows fully developed muscular coat. The medial cells not morphologically different from ordinary smooth muscle cells	Mesenteric and other branches of aorta show well developed media, although the differentiation of the cells is not as far advanced as in the aorta

* See photograph, Fig. 6.

† See photograph, Fig. 7.

used the human embryological collection of the Carnegie Institution. Embryos ranging in age corresponding to lengths of 11 mm. to 78 mm. were studied in serial sections to determine at what age the differentiation of the muscular coat of the arteries occurred, and if any pecu-

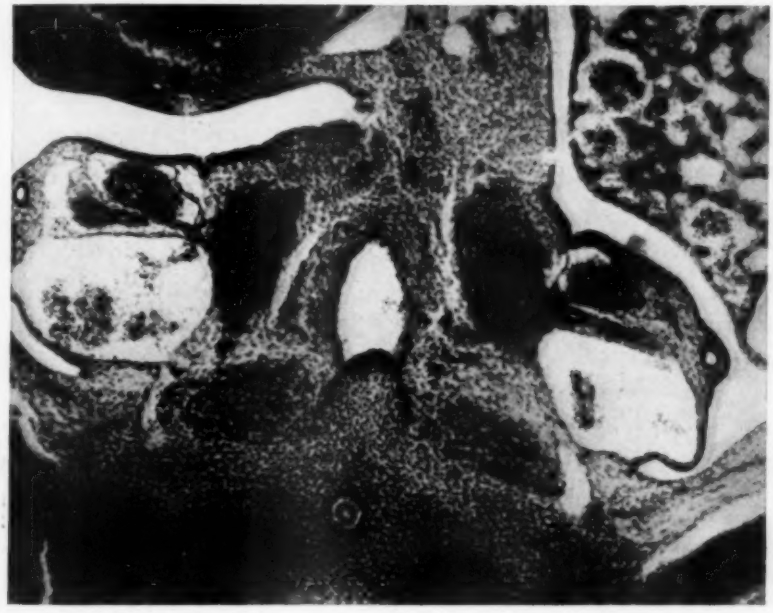

FIG. 6. EMBRYO NO. 1836. A LOW-POWER MICROPHOTOGRAPH OF THE AORTA AND TWO INTERCOSTAL ARTERIES FROM A HUMAN EMBRYO, 11 MM. IN LENGTH

The aorta and its branches consist of simple endothelial channels about which there is a slight concentration of mesenchymal cells which later form the muscular coat of the vessel. Compare with Fig. 7.

liarity of development of the muscularis could be found which might account for the imperfection of the vessel wall at the point of bifurcation. It was thought best at first to study the cerebral vessels but after examination of embryos at a very early age, in which muscle could already be seen in many small vessels, it was found more satisfactory

and quite as practical for the purpose of gaining the desired information to confine our observations to the aorta and its immediate branches. Since the aorta is easily recognizable and its course followed satisfactorily in very young embryos, the development of its wall from the

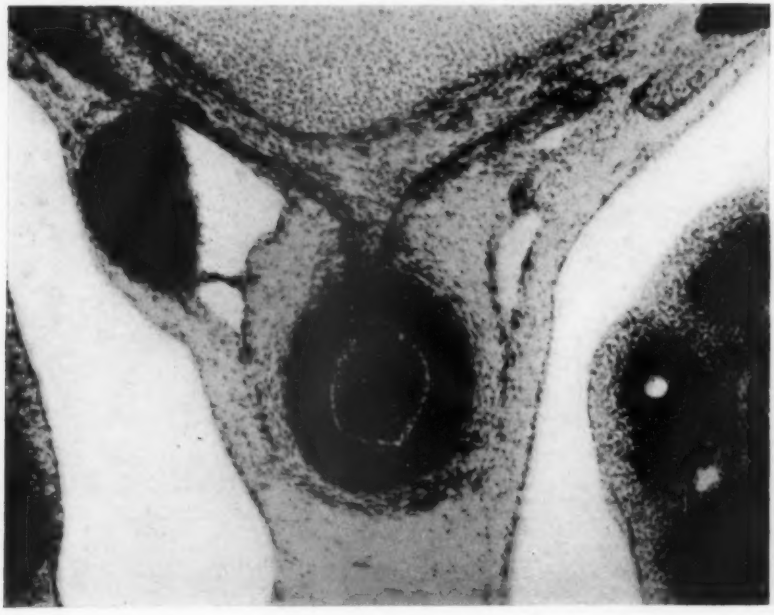

FIG. 7. EMBRYO NO. 3669. A LOW-POWER MICROPHOTOGRAPH OF THE AORTA AND TWO INTERCOSTAL ARTERIES FROM A HUMAN EMBRYO 34 MM. IN LENGTH

At this stage of development the media of the aorta has become recognizable as such, while the intercostal arteries remain as simple endothelial channels. Compare with Fig. 6.

simple endothelial tube to the highly organized muscular channel with its branches can readily be followed. In the accompanying Table III we have summarized the observations made on the various embryos.

The aorta, as well as all other vessels, is first recognized as a simple

endothelial tube about which lie totally undifferentiated mesenchymal cells. One embryo as young as 11 mm. (Fig. 6) showed already an irregularly arranged mass of these cells concentrated about the endothelial aorta. As one proceeds with the examination of embryos of progressively increasing lengths this concentration of mesenchymal cells becomes more and more regularly arranged, and the individual cells assume a circular distribution. In embryos of 34 mm. length (Fig. 7) the aortic wall presents all the characteristics of a fully developed vessel in so far as its anatomical structure is concerned. The cells forming the media have all the appearances of circularly disposed muscle cells. No elastic tissue, however, can be recognized and no micro-chemical proof that the cells forming the media are true, fully developed, muscle cells was possible because of the nature of the material. The intima is represented by the endothelial lining and the adventitia by fairly well differentiated connective tissue. While this condition exists in the aorta, the smaller branches of this vessel still remain as simple endothelial channels without even a nearby concentration of mesenchymal cells. The endothelium of the branches is directly continuous with that of the aorta but in the aorta the media stops sharply at the point of exit of the branch.

The development of the wall of the branches of the aorta can perhaps best be seen in the mesenteric artery which becomes recognizable quite early in comparison with other branches and which is a well developed muscular structure where the intercostal arteries, for instance, still exist as tiny endothelial sprouts from the aorta. The process through which this vessel passes in the development of its muscularis is identical with that of the aorta. The point of most interest and importance in this development is that the muscle cells from which develops the muscle sheath have their origin in undifferentiated mesenchymal cells which surround the branch itself and which develop quite independently of the older aortic muscle cells.

The independence of development of the muscularis of a major vessel and that of a primary branch deserves emphasis since it offers at least a theoretical explanation of the muscularis defect at the point of bifurcation of the vessels. The idea that the two independently developing muscular coats fail to fuse completely at the junction of the two vessels presents itself at once as the source of the muscularis defect. That

such a thing happens we may regard as possible, although one may not be able to demonstrate it. Just why the defect should always be localized at the apex of the acute angle and not elsewhere of course finds no adequate explanation in this theory. Doubtless there may be other factors such as rate of growth of tissue supplied by the aortic branches and a consequent tendency to spread the angle of bifurcation, thus permitting a gap to occur in the acute angle while encouraging an approximation of the media of the aorta and its branches in the obtuse angle formed by the division.

Having discussed at some length the nature and origin of the muscularis defect, there remains still to be answered the question regarding the significance of this structural imperfection. This absence of muscle at the point of bifurcation of the arteries can have but one meaning and that is that it constitutes a *locus minoris resistentiae* in the vessel wall at a point where miliary aneurysms of these arteries are prone to occur.

Of such an anatomical imperfection in the arterial structure we have not been able to find any note in the literature. There are, however, certain vascular peculiarities which have been described by Busse, Emrich and Kerpola which may have some relation to our muscularis defect, although, as far as we can judge from their description, they are not identical. We refer to the papers of Busse (2) and Emrich (3) on the origin of the so-called "Dehnungs-aneurysmen", and to that of Kerpola (22) on the pathology of miliary aneurysms of the cerebral vessels.

Busse and Emrich studied that area of the cerebral circulation comprising the anterior communicating artery and its connection with the two anterior cerebrals. They came to the conclusion, after studying a large number of cases, that the so-called "Dehnungs-aneurysmen" are the direct result of developmental anomalies in the vessel walls which are responsible for areas of lowered resistance to blood pressure. They state that the development of the anterior communicating artery is a complicated process, during the course of which many vessels of smaller calibre become obliterated, while others fuse to form the permanent channels. They found concrete evidence of this in the presence of fibrous cords, which they believed to be obliterated blood channels, attached to the vessels in the area of the anterior communicans and

the adjacent portions of the anterior cerebral arteries. They likewise found great complication and variability in the structure of the anterior communicating artery which seemed to them to be additional evidence of an extraordinary method of development of this area of the cerebral arterial system. To the complicated changes that take place in the formation of the anterior communicating artery they attributed irregularities in structure of the vessel wall, such, for instance, as great thinning out of one or all three coats of the artery. Again, at points of attachment of the fibrous cords, the preëxisting vessels, they described some alteration in structure of the wall, pointing out in some instances interruptions of the muscular coat. It is very possible that the "Dehnungs-aneurysmen," which we know as localized, more or less saccular, dilatations of the vessel wall, in which all the normal coats are present, may have their origin in the complicated course of formation of the vessel wall, in the region of the anterior communicans, as described by Busse and Emrich. These authors, however, point out a connection between the disturbance in the structure of the muscularis at the point of attachment of the obliterated vessels, and the formation of true saccular aneurysms. They regard the aneurysms as first represented by a localized dilatation of the vessel wall, all the normal coats being present, that is, a "Dehnungs-aneurysma." This simple dilatation, they think, is followed by degeneration of the muscularis and elastic membrane, with an accompanying intimal proliferation, the end result of which is an aneurysm whose minute structure is that which we have described in our cases. Busse and Emrich mention the fibrous cords and the accompanying "hypoplasia" of the vessel wall at their points of attachment to the larger vessels, in connection with practically all the larger vessels forming the circle of Willis. They state that this hypoplasia is to be found especially at the point of bifurcation. Since we have never seen the fibrous cords in relation to our medial defect at points of division of the vessels and since the descriptions of Busse and Emrich are somewhat meagre, we are inclined toward the belief that the medial defect which we describe in this paper is probably quite different from that structural peculiarity to which these two authors refer.

Ample support of the ideas of Busse and Emrich as to the possibility of the occurrence of congenital defects in the structure of the cerebral

vascular system is to be found in Streeter's (23) study of the development of the venous sinuses of the dura, from which it is evident that almost any variation in gross structure is possible. From what Streeter says, the remarkable thing is that the structure of the cerebral vascular system, from case to case, is so constantly the same. With gross variations so highly possible it is not the least surprising to find minute variations in cerebral arterial structures of the kind described by Busse, Emrich and ourselves.

It is probably not so difficult to interpret the findings of Kerpola who, in striking contrast to practically all other workers in the field of cerebral aneurysms, made a rather detailed study of the vessels in his cases of aneurysms, which were not associated with the lesion itself. Kerpola described degeneration of the media especially at the point of exit of small vessels from the main cerebral channels. Such degenerations, he states, are replaced by connective tissue and are accompanied by proliferative changes in the intima and degenerative change in the internal elastic lamella. He emphasizes the degeneration of the media as the primary alteration in the vessel. Such a description, except for the suggestion that the medial change is primary, points at once to an arteriosclerotic process, and it is, indeed, with this process that this writer identifies the vascular change to which he attributes the formation of aneurysms. One needs only a glance at the description of our muscularis defect, and a moment to recall the details of the arteriosclerotic process, to be convinced that Kerpola's vessel changes bear no real similarity to our muscularis defect but that they do represent the outcome of ordinary arteriosclerosis.

Before proceeding to another topic of discussion, it is worth while to refer to certain pecularities in the structure of the veins which are interesting but have no definite bearing on the problem under consideration. A conspicuous variation in the thickness of the muscular coat of the veins has been described by Backman (24). In young individuals veins which lay adjacent to bone and muscle, and other comparatively non-elastic and rigid tissues were found to have either no muscle whatever or greatly attenuated muscular coats in that portion of the wall lying next to the non-elastic tissue. This unusual condition he regarded as of developmental or adaptive origin, and while considered quite normal under certain circumstances, it was thought to have some

bearing upon the formation of varices. Interestingly enough the same venous structure has been described in animals by von Baum and Thienel and again by Bärner, according to Backman. In the papers of Kraemer (25) and Hasebrook (26) may likewise be found reference to variations in the structure of the veins, especially as related to the formation of varices. Hasebrook described long tumor-like malformations in the walls of the vein, which have become extremely dilated, to which he ascribes some significance in the formation of this dilatation. Kraemer noted peculiarity in the structure of the venous wall at the point of attachment of the valves. We ourselves have made no study of the veins, nor have we gone into the literature with sufficient thoroughness to speak with any authority on the character and significance of the peculiar structural condition which we have just noted. However, that they should not be regarded as the same hypoplasia which we have described in the arteries seems reasonable to assume from the descriptions recorded.

IV

It has been shown that the dividing points of arteries constitutes a weak point in the vascular system because of the presence of a muscularis defect within this area. The characteristic location of this defect in the acute angle formed by the dividing vessel, and the fact that miliary aneurysms are most often found at the same point, naturally suggest that there may be some connection between the two. Since the formation of any aneurysm depends essentially upon the pressure to which the vessel wall is subjected, under *normal conditions* of arterial blood pressure, an aneurysm should occur at the weakest point in the system unless the mechanics of the circulation should be such as to cause the pressure at the site of the defect to be lower than that at other points in the same area. In order to gain some information about the distribution of pressure within the area of bifurcation of the arteries and at the same time to learn something of the strength of the arterial wall at different points, two experiments were performed as follows:

Experiment No. 1. In this experiment the cerebral arteries were subjected to breaking pressure in order to determine whether the site of rupture would always be found at the point of bifurcation, the char-

acteristic location of the muscularis defect. Six different segments of the two middle cerebral vessels of a single case were selected, each segment including a fork. These segments were isolated *in situ* by ligatures, a cannula connected with a syringe being securely fastened in the mother vessel. Sufficient pressure was exerted upon the syringe plunger to cause the vessel to rupture. The pressure was not measured, but the rupture point proved to be unquestionably beyond the blood-pressure normal to arteries of the size being tested. In not a single instance did the rupture occur in the fork. The point of rupture, however, was always in the area near the bifurcation.

On first thought this experiment offered considerable disappointment, but when the various conditions are taken into consideration the results are not surprising, and the validity of the experiment for demonstrating a significant weakness at the site of bifurcation becomes indeed questionable. In the first place, the experiment is an acute one which involves the strength of inert tissues as demonstrated by a resistance to a pressure abnormally high. Secondly, one deals with a stationary fluid under very high pressure, in which case the pressure at all points within the system is the same, whereas under normal conditions of circulation the pressure-exerting fluid is under comparatively low pressure, is in motion and is pulsating, the movement of the column of fluid being directed toward the supposedly weak point in the vessel wall. A third criticism is that one must rely on chance so far as choosing a segment of vessel with a muscularis defect is concerned. The impossibility of finding a segment of vessel without tiny branches which must be torn in the manipulation incident to arranging the ligatures and at the origin of which there may be a muscularis defect, is a fourth consideration which makes the experiment impracticable. Furthermore, rupture of the vessel precludes any satisfactory microscopic study for control. Because of so many criticisms it was not thought useful to proceed with the examination of other cases by this method, and the results of this one experiment are thought to be of no significance.

Experiment No. 2. Our second experiment was carried out for the purpose of determining the comparative pressures at different points in the arterial wall, all within the zone of bifurcation of the vessel. Since it was not practical to use the vessels themselves we constructed

a number of branching glass tubes as pictured in Plate I. In each of these an attempt was made to vary the angle of bifurcation between the extremes of a straight angle and an acute angle of the maximum degree possible with the material being used. Small openings were made, one in each angle and all of the same calibre. Care was exercised to have the relative position of outlets II and III as nearly the same as possible, while outlet I was always placed in such a way as to make its long axis parallel to and continuous with the long axis of the branch of the fork chosen to represent the parent vessel. The two branches of the parent vessel were constructed with individual calibre equal to that of the parent vessel. In one branch of the parent tube a second set of small openings was made as pictured in Fig. G.H., etc.

The apparatus just described was fastened securely to the laboratory table so that all branches of the system lay in a horizontal position. The system was connected with a water hydrant so that water under easily variable pressure but not pulsating might be caused to enter through one of the three arms of the fork. For the sake of description, the entering arm is regarded as the parent vessel. The small outlets designated as I, II, and III, etc., were connected by short rubber tubes, all of the same calibre, to water manometers so arranged that simultaneous readings of registered pressure might be easily and quickly made.

In order that a continuous flow of fluid through the system might be maintained, thus making the system for practical purposes similar to a segment of the arterial tree, at least one of the branches was always allowed to remain open. Under such conditions two principal pressure elements must be considered as existing within the system, namely, pressure head or lateral pressure and velocity head or that pressure due directly to the movement of the fluid. It was realized in the experiment that by changing the direction of flow within the various systems there would be brought about a simultaneous variation or change in the pressure relationships, since the way the pressure components affect the given points must be thereby changed. We were not unmindful of the possibility that the shape and general conformity of the various parts of the stream-bed might materially influence the distribution of pressure, and in order to offset this obviously variable factor, the fluid was passed through each system in every possible way, the pressure

measurements in the various outlets being recorded for each hook-up. Since the pressure relationships as found in all these different hook-ups were in principle identical with those determined in hook-ups as shown in Figs. A, G, S and M, for the sake of brevity only the data obtained in these hook-ups is given in Table IV.

In such a system as we have constructed, and in fact in the corresponding segments of the arterial tree, it might seem at first quite possible to predict that the total pressure exerted upon the point in the wall of the system corresponding to the apex of the angle of bifurcation would be greater than that at any other point in that same segmental area. Certain formulae have been devised in studies in hydraulics

TABLE IV

Relative pressures at points designated under conditions of flow of water through system of glass tubes illustrated in Plate I

FIGURE	WATER				
	I	II	III	IV	V
	cms.	cms.	cms.	cms.	cms.
A	58.4	42	43		
G	73.4	55.2	57.6	59.9	59.9
M	68.4	55.6	55.6		
S	74.3	59.6	60.4		

which might be useful in determining approximately the pressure values at the desired points. Since, however, these formulae are accurate only under certain specified ideal conditions, and especially since they have been derived from determinations made in uncomplicated straight tube systems, it is safe to say that they could not be applied to a problem such as that presented by our branching system except in a purely qualitative way.[2] The disturbance in the flow of the particles of fluid, with the consequent incidence of subsidiary currents and other unpredictable forces attending the change in direction of the moving column of fluid in the area of bifurcation of the system, makes it advisable if not imperative to depend on actual experiment for determination of pressure relationships at the points in question.

[2] We are indebted to Mr. Frederick Medaugh, of the Department of Civil Engineering of the Johns Hopkins University, for his aid in connection with the hydraulic aspects of this problem, and to Dr. Joseph S. Ames for his criticisms.

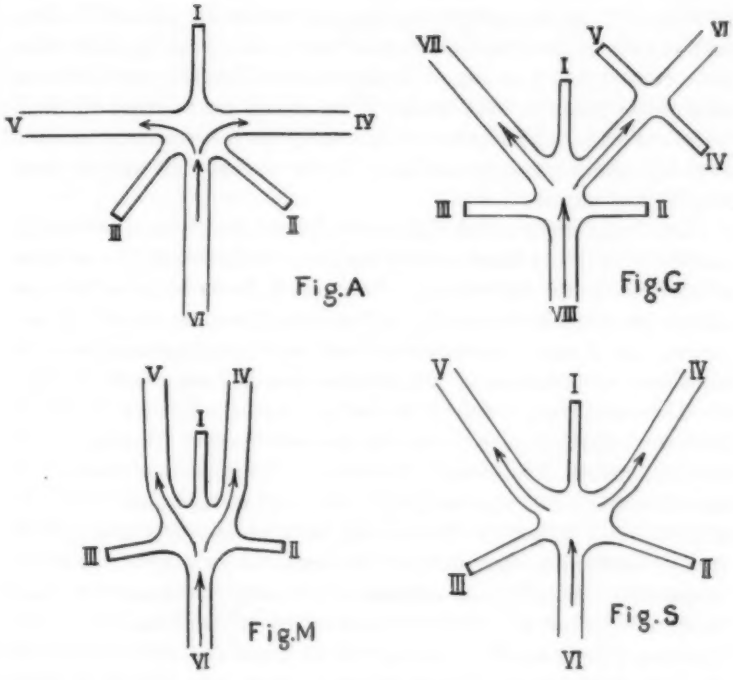

PLATE I

ACCURATE DRAWINGS OF FOUR DIFFERENT GLASS TUBE FORKS USED IN DETERMINING THE RELATIVE PRESSURES AT THREE DIFFERENT POINTS IN THE AREA OF BIFURCATION

The arrows indicate the direction of flow of the fluid (water). The small side tubes designated I, II and III were connected to manometres from which simultaneous readings were taken under conditions which were varied by changing the velocity of flow through the system from very high to very low. See Table IV for numerical data.

The experiment as carried out shows unmistakably that the suspected difference in pressure at the designated points in the area of bifurcation does exist. The results of the various measurements are summarized in Table IV. In interpreting the figures given in this table, it is necessary to keep in mind the direction of flow of the current as pictured in the corresponding drawings of the apparatus in Plate I. Simultaneous manometer readings were made. The figures are in terms of centimetres of water and represent the average of five readings for each hook-up, under pressure conditions in the parent tube varying from very high to very low.

There is obviously a wide difference between the physical conditions as they exist in the blood vessels and those obtaining in the artificial system used in the experiment. As we see it, however, this difference has no great significance so far as the principle demonstrated is concerned, but it may have important influence upon quantitative relationships. Two factors of special interest are, of course, the element of resistance offered to flow of the medium, and the fact that the blood flow is a pulsating stream, whereas the movement of the water in the artificial system is constant. Resistance in the blood vessels must be exceedingly low in comparison with that in glass tubes, and hence, for a given head, velocity of flow would be considerably higher, this in turn producing a greater difference between the pressures at the points in question. Whether the difference in viscosity between blood and water would offset this effect by retarding the stream is not easy to say. It seems quite possible. Because of the pulsating character of the blood flow, the factor of waterhammer comes into play to increase the difference in pressure at the points under consideration. This factor would increase in significance as the angle of bifurcation increased, becoming a maximum when the angles reaches 180°. Without actual measurements of these factors it is, of course, impossible to be sure of their effect, but it appears that the sum total of them all would be to accentuate the difference in pressures which the experiment demonstrates.

From the results of the experiment, the following conclusions may be drawn:

A. The point of maximum pressure is always that corresponding to that point in the vessel wall where the longitudinal axis of the impinging column intersects the vessel wall.

B. The difference between the pressure at different points increases as the velocity of the stream increases, and as the size of the angle of bifurcation increases.

C. Where the differences between pressure at any given points are very small, (1 or 0.5 cm. water) side currents or eddies may cause a reversal of the expected relationship.

D. At a velocity in the parent vessel sufficient to cause at the point of intersection of the axis of the stream and the vessel wall a pressure equivalent to 91 mm. of mercury (diastolic blood pressure), the pressure at the junction of parent vessel and its branches is equivalent to 68 mm. of mercury. This difference of 22 mm. of mercury is then the measure of difference between the pressure at a point corresponding to the medial defect which we have described and that at a point in the opposite wall corresponding to the apex of the obtuse angle formed by the dividing vessel, under the stated conditions.

From the experiments just recorded and from the demonstration of a structural defect in the arterial wall at the acute angle formed by the bifurcation of vessels, it appears that conditions are such as to favor the formation of aneurysms. This muscularis defect we have come to regard as the basic factor in miliary aneurysm formation since, because of its presence, a weak area exists in the arterial wall at a point where, as experiment has shown us, a maximum strength is required. That there must be a fundamental connection between the muscularis defect and aneurysm formation is emphasized by the often repeated observation that these miliary aneurysms are found characteristically in the angle formed by the branches of vessels of medium size.

All our observations have led us to consider the development of a miliary aneurysm as proceeding through the following steps:

1. Physiological localized saccular dilatation of the arterial wall at the point of bifurcation which varies in degree depending upon the blood pressure and the resisting strength of the defective vessel at this point.

2. Proliferative reaction of the intima resulting in a fibrous plaque at the site of the physiological dilatation, perhaps an attempt to re-establish the regular continuity of the vessel wall and to compensate for the existing weakness of the wall, or else a reaction to injury produced by irregular currents within the dilatation.

3. Degeneration of the internal elastic lamella—a gradual process eventuating in total disappearance of this membrane.

4. The formation of a persistent saccular dilatation, the result of partial loss of resistance and elasticity of the vessel wall accompanying degeneration of the elastic tissue.

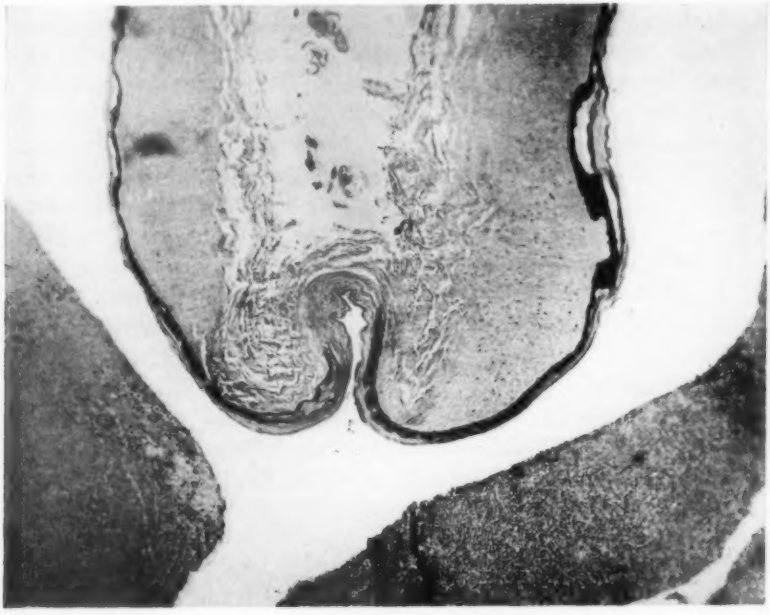

FIG. 8. CASE NO. H-10793. EARLY STAGE IN THE FORMATION OF A MILIARY ANEURYSM, SHOWING DEGENERATION OF THE INTERNAL ELASTIC MEMBRANE OVERLYING A DEFECT IN THE MEDIA IN THE ACUTE ANGLE FORMED BY A DIVIDING MIDDLE CEREBRAL ARTERY

5. Final partial or total thrombosis of the sac with subsequent organization and calcification, or progressive increase in the size of the sac with rupture and fatal subarachnoid haemorrhage.

Given the muscularis defect and a local blood pressure favorable to aneurysm formation, a moment's consideration of this succession of events is sufficient to center one's interest upon the elastic lamella as a

factor of the greatest significance. Since, as is obvious, the development of an aneurysm at any given point depends upon the condition of the elastic tissue, we feel justified in giving some thought to this relationship.

We feel secure in speaking of the absence of the internal elastic membrane as the result of a degenerative process, for we have seen this in

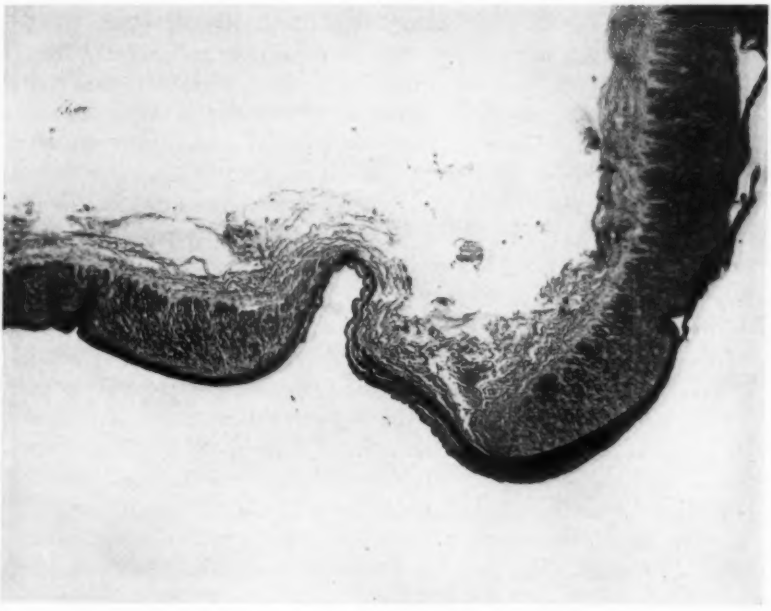

FIG. 9. CASE NO. H-10668. EARLY MILIARY ANEURYSM FORMATION, SHOWING CHARACTERISTIC MEDIAL DEFECT, AND DEGENERATION OF THE INTERNAL ELASTIC MEMBRANE WITHOUT SIGNIFICANT ALTERATION OF THE INTIMA
The section is from the point of division of a middle cerebral artery

sections from our case No. H-10793 (Fig. 8). In this connection may be added the following note from another case, No. H-10668 (Case No. 5, Table I), since this case, along with H-10793 illustrates quite clearly the earliest stages in aneurysm formation.

The aneurysm (Fig. 9), accidentally discovered, could be seen in the

gross as a thin, slightly bulging area exactly in the fork formed by the primary branches of the middle cerebral. The aneurysm wall was composed of fibrous cellular tissue which obviously belonged to a fibrous intimal proliferation at this point, outside of which lay the adventitial coat of the vessel. This layer was of normal thickness. Lying between the fibrous intimal layer and the adventitia were fragments of elastic tissue in an extraordinary state of degeneration. That the elastic membrane did not break suddenly was clearly demonstrated by the characteristically staining granular degenerative debris resulting from the slow disintegration of the elastic tissue. The well preserved ends of the elastic membrane extended into the aneurysm wall for a short distance, and never, in many sections cut serially, showed any evidence of splitting, duplication, fraying out, etc.

This is the only case in which we have seen the development of miliary aneurysms actually in progress, where the development of the aneurysm was unassociated with any other process. The early degeneration of the elastic membrane associated with some thickening of the intima was seen in Case H-10793, as cited above.

The cause of the elastic tissue degeneration we must frankly admit we do not know. That the absence of elastic tissue in the walls of the completed aneurysm has any connection with a malformation of the vessel wall, in the course of which the elastic tissue has been left out, can be definitely denied on the basis of two observations which can hardly be questioned, namely, first that in our study of arteries from many cases we have never seen absence of the internal elastic membrane, although absence of muscle has been frequently met with, and second, that in the aneurysms which we have seen in the process of development the elastic membrane may still be clearly demonstrated, although it be in a poor state of preservation. These facts deserve emphasis because of the contention of some of the earlier workers, especially Eppinger (1), that miliary aneurysms had their origin in congenital defects in the internal elastic membrane. This viewpoint was advanced in spite of the fact that apparently no such defect had ever been seen in the arteries outside of the walls of the aneurysms. Eppinger repeatedly emphasizes the fact that in his cases the vessel walls were normal everywhere except in relation to the aneurysm. The whole contention seems to have been based on the fact that the elastic tissue ceased abruptly at the margin of the aneurysm.

One cannot exclude the possibility of a connection between arteriosclerosis and elastic tissue degeneration. Indeed, arteriosclerosis is considered by some as the basis of development of cerebral aneurysms. As everybody knows, extreme sclerotic changes may so affect the vessel wall as to leave no semblance of the normal architecture. The muscularis may completely disappear, the adventitia become thick and hyaline, the intima piles up so as to tend to obstruct the lumen of the vessel, and lastly, the internal elastic membrane may split up and become so ragged as to be quite useless as an elastic body or a pressure-resisting mechanism. Strangely enough, however, one rarely if ever sees such a combination of changes in connection with aneurysms of the cerebral arteries. What one does see is the granular diffuse degeneration of the elastic membrane, sometimes with segmentation, underlying intimal thickenings (See Case No. H-10793). The presence of thickened intimal plaques within the aneurysm has been thought by many workers to appear after dilatation of the vessel wall has taken place, and they have therefore regarded the greatly thickened intimal sheath as either a compensatory mechanism or as the result of overgrowth of intimal cells stimulated by abnormal currents within the sac. Nevertheless, one cannot deny that the intimal change sometimes, at least, antedates dilatation. If the intimal plaques do come after a physiological dilatation has occurred, then one cannot exclude them as a factor in bringing about the subsequently developing degeneration of the internal elastic membrane. In spite of all these possibilities, however, we are able to say definitely that degeneration and disappearance of the elastic membrane may occur in the absence of a sclerotic plaque as is shown by the following observation from aneurysm Case No. 9, B.V. X-2, Table I.

The aneurysm in this case was microscopic in size and was discovered accidentally in our search for muscularis defects. Its microscopic structure was different from other aneurysms in this series since its walls were composed of nothing but adventitia, no change whatever having occurred in the intima. No muscle and no elastic tissue membrane was present in the wall of the sac. The vessels forming the fork in which this aneurysm lay were extremely sclerotic, segments of these vessels near the opening of the aneurysm showing thick hyaline intimal plaques (See Fig. 10).

Certain degenerative changes in the elastic tissue in the blood vessels is known to occur in some of the acute infectious diseases. A discussion of this condition may be found in the papers of von Wiesel (27). There seems to be so little similarity between the conditions under which these changes occur and those attending aneurysm formation that it seems sufficient here only to mention the possibility for the sake of completeness.

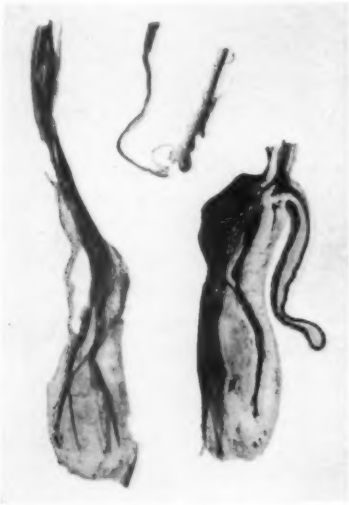

FIG. 10. CASE NO. B.V.X-2. MILIARY ANEURYSM FULLY DEVELOPED AT THE DIVIDING POINT OF A MIDDLE CEREBRAL ARTERY, TOTALLY UNASSOCIATED WITH SCLEROTIC CHANGES IN THE INTIMA
Sclerotic changes elsewhere in the vessel walls are extreme

A mechanical factor as the cause of degeneration of the internal elastic membrane must be accorded a place of importance in spite of the fact that we cannot bring to bear concrete evidence to support the idea. One can say with at least theoretical certainty that the localized over-distention of the elastic membrane, arising from the fact that it is necessary for this membrane to bear the whole burden of resisting blood pressure, in the absence of any support from the defective media, may

lead either to sudden rupture of the membrane or else to its gradual disintegration. We can find no objection to this explanation of the disappearance of the elastica from the aneurysm wall, something which we cannot say of other explanations.

What we have said of the structure of the cerebral vessels in relation to aneurysm formation may be applied as well to the vessels of the mesenteric and coronary arteries. The weak spot has been shown to exist at the bifurcation of these arteries just as it does in the cerebral vessels. That aneurysms should occur in these arteries is not only to be suspected but has already been demonstrated in several observations, good examples of which are to be found in the studies of Eppinger (1) and Gee (20). In the course of our routine pathological studies muscularis defects have been seen from time to time in the arteries of the kidneys and of the pulmonary system. That this medial defect should be associated with all vessels of the body would seem to be expected in view of its embryological development. The finding of multiple small aneurysms especially located at points of division of the small pulmonary arteries as reported by Wilkins (21) and what is of greatest interest, the finding of aneurysms of the same character attached to practically all the conspicuous vessels of the body, as described in one of Eppinger's cases, would seem to emphasize still further the fact that the muscularis defect is a most widespread structural imperfection and that its relationship to aneurysm formation is not peculiar to the cerebral circulatory system.

Our interpretation of the facts, as we have stated it in this account of multiple miliary aneurysm formation, forces us to the conclusion that multiple aneurysms of the superficial arteries of the brain, as well as those of the arteries of medium size of other organs, are acquired lesions based upon a fundamental predisposing factor in the form of a congenital arterial structural imperfection, a defect in the muscular coat, characteristically located at points of bifurcation.[3]

[3] In the conclusions of our preliminary report of this work, as published in the *Centralblatt für Allgemeine Pathologie und Pathologische Anatomie*, 1928–29, V. 44, p. 243, we have written as follows: "Mit dem Nachweis des mangelhaften Baues der Arterienwand an einzelnen Teilungsstellen ist meiner Ansicht nach ein konkreter Beweis dafür geliefert, das sowohl die multiplen kleinen Aneurysmen der basalen Arterien des Gehirns, als auch die der verschiedenen anderen kleinen

While maintaining this viewpoint, we do not for a moment deny that small aneurysms may arise from other causes, such, for instance, as arteriosclerosis, syphilis and other inflammatory diseases. An arterio-

FIG. 11. CASE NO. B.V.-3816. SMALL ARTERIOSCLEROTIC ANEURYSM OF THE CAROTID ARTERY AT THE BASE OF THE BRAIN

The position of the aneurysm, not in the acute angle formed by the branches of the main channel, is so atypical of the true miliary aneurysms that this fact alone would exclude it from this group without the necessity of pointing out the extreme arteriosclerosis associated with both the aneurysm itself and the vessels from which it arose.

sclerotic aneurysm we have ourselves seen and have included it here for the sake of comparative study. If one refers to Fig. 11, the photograph of this aneurysm, and compares this with the miliary aneurysm

Arterien in ihrer Anlage, aus der Entwicklungszeit stammen, also angeboren sind, eine Meinung, die zwar oft ausgesprochen wurde, der bis jetzt aber jede sichere Grundlage fehlte."

pictured in Fig. 2, the essential differences between the two types are at once apparent. As for syphilis and other inflammatory diseases, it need only be said that aneurysms in the course of such diseases of the arteries are so characteristic that they need never be confused with the typical multiple miliary aneuysms.

It seems appropriate to mention at this point a condition which may be considered somewhat analogous to aneurysm formation as based upon a developmental imperfection in the vessel wall. We refer to the form of focal dilatation of the intestines, commonly termed "false diverticulum." These diverticula occur always in great numbers and arise from that portion of the intestinal wall through which the larger vessels enter. A total interruption of the muscular coats, longitudinal and circular, is aways demonstrated at such places and it is this fact that apparently explains the absence of these layers in the walls of the diverticula. The only muscle demonstrable in such diverticula is that easily identified as muscularis mucosae. It is generally believed, and it seems correctly so, that these diverticula do not exist as malformations *per se* but develop as the result of pressure within the intestine produced by peristaltic movements. Such lesions are sometimes regarded as herniae of the mucosa and submucosa through the muscular layers and in like manner perhaps we might think of the miliary aneurysms in their earliest stages, before degeneration of the elastic membrane, as herniae of the intima and elastica through a gap in the muscularis.

SUMMARY

In the course of a study of a group of cases of miliary aneurysms of the cerebral arteries, we have found a hitherto undescribed peculiarity in the structure of the wall of the arteries, upon which it would appear that the formation of miliary aneurysms depends. This peculiarity consists in a muscular defect in the media located in the portion of the vessel wall forming the angle of bifurcation. This medial defect was sought for in arteries other than those of the brain and found to be present in cases where there were no aneurysms. Such defects were noted, for example, in the coronary and mesenteric arteries. The frequency of occurrence of the medial defect in normal as well as pathological cases was found to be sufficiently great to indicate that the

peculiarity in structure at the point of bifurcation is a relatively normal arrangement.

It has been possible to show that the muscularis defect as such dates from embryonic life. From a study of the time and mode of development of the muscular coat of the arteries, we have arrived at a possible theoretical explanation of the failure of muscle development at the angle of bifurcation. This is to be found in the observation that the muscular coat of any given vessel develops from a group of mesenchymal cells quite separate and distinct from those which form the muscularis of the branches of that vessel, and that the muscular sheath of the parent vessel develops at an earlier period than that of its branches. A failure of the two separately developing muscle coats to fuse properly seems to offer at least a possible explanation of the later observed defect.

That the malformation of the artery wall at the point of bifurcation underlies the later development of aneurysms appears to be indicated by the following facts.

1. Wherever aneurysms of the miliary type are present, they always occupy the angle formed by a branching artery.

2. The defect in the arterial wall is always located at the bifurcation and at the point where miliary aneurysms occur characteristically.

3. The muscularis defect constitutes unquestionably a *locus minoris resistentiae* in the wall of the vessel.

4. We have demonstrated experimentally that the point of maximum pressure in the vessel wall under normal conditions of circulation in the segment represented by the dividing point is that point corresponding to the location of the muscularis defect.

5. In all cases in which we have found aneurysms of the cerebral arteries we have also found conspicuous medial defects at points of division of the cerebral vessels.

6. In none of the aneurysms studied in this series can muscle be demonstrated in the wall of the sac, although the series includes aneurysms in all stages of development from the earliest out-pouching of the vessel wall to great saccular dilatation and rupture. This finding is in accord with that of other investigators who have studied these aneurysms.

While the evidence at hand indicates that the muscularis defect

constitutes the groundwork for miliary aneurysm formation, there are convincing facts which cause us to regard the strength and persistency of the internal elastic membrane as a factor of greatest significance in the development of anatomical aneurysms. While it is conceivable that small diverticula at the point of bifurcation may occur while the internal elastic membrane is still intact, it seems that no anatomical aneurysm can develop without disintegration of this membrane. In our study it has been possible to rule out all known causes of elastic tissue degeneration except the traumatic factor of over-distention due to blood pressure. This we regard as the essential cause of the internal elastic membrane disintegration which we have found constantly in the miliary aneurysms.

In summarizing our observations it seems justifiable to say that miliary aneurysms of the superficial cerebral arteries and most probably those of all other arteries of medium size occur quite independently of any inflammatory process, arteriosclerosis, or external trauma, and that these aneurysms as such are not congenital malformations. That they are acquired lesions arising from a combination of focal weakness in the vessel wall, resulting from a congenital muscularis defect, and degeneration of the internal elastic membrane, due to continued over-stretching of this membrane, seems to us the most logical conclusion.

While maintaining this viewpoint we are not unmindful of the fact that there are aneurysms of the small vessels due to arteriosclerosis, trauma, syphilis, bacterial infection, etc. These aneurysms, however, as we have seen them, are sufficiently characteristic to allow easy recognition and hence they need never be confused with those of the specific group which we have been discussing, and which themselves are so characteristic in their location, multiplicity, size, microscopical structure, and other characteristics.

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THE NUMBER AND SIZE OF THE GLOMERULI IN THE KIDNEY OF SEVERAL MAMMALS[1,2]

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In the past numerous investigators have determined the number of glomeruli in the kidneys of various mammals usually by one of three general methods; *viz.* (1) serial section either with total count or some method of estimation from sample counts, (2) the Janus green technique of Nelson (1922), and (3) injection with prussian blue reagents, maceration, separation of the cortex and counting *in toto* or on weighed portions (Vimtrup, 1928). In the last two procedures, the counting is made on small bits of tissue pressed out on ruled slides. The literature has recently been summarized by Vimtrup (1928) and by von Mollendorf (1929). Numerous discrepancies exist, and no systematic study of the glomerular development of different mammals has been made.

While determining the number of renal corpuscles in the bird's kidney by a procedure suggested by Doctor E. K. Marshall; namely, injecting the kidneys with prussian blue reagents, macerating in hydrochloric acid, taking a small portion of the macerated organ at a time into a ruled, flat-bottomed Syracuse dish, teasing, and finally counting the number in each dish under the binocular dissecting microscope, the following simple method of determining their number was found feasible.[3]

The kidney is first washed free of blood with physiological sodium chloride solution, containing a trace of sodium nitrite, through the renal artery and then injected with a mixture of equal parts of 2.5 per cent aqueous potassium ferrocyanide and 2.5 per cent aqueous

[1] Granted the William H. Howell Award, June, 1930.

[2] Submitted for publication, June 13, 1930.

[3] Dr. Marshall informs me that Dr. Nash, at the New York Medical School, has independently developed and been using a somewhat similar sampling method for counting glomeruli in fish kidneys.

ferric ammonium citrate. A pressure of approximately 6 feet of water is used. The organ is then placed in a solution of equal parts of water and concentrated hydrochloric acid for a period of time varying from 10 hours in the case of the rat kidney to 40 hours in that of the ox kidney. When dealing with large kidneys maceration is better if they are cut into pieces between 1 and 2 centimeters thick. Maceration must be more prolonged than is usual when the preparation is for teasing. From the acid the organ is transferred to distilled water after being washed gently in tap water. Here it may remain several days if a few crystals of thymol are added. The duration of maceration and standing in distilled water is ideal when the kidney will fall apart easily when gently taken up into a pipette the diameter of whose mouth is two millimeters.[4] With such a pipette the entire kidney is transferred to a measuring flask and the contents diluted to a known volume. The resulting suspension is stirred and 2 cc. are accurately pipetted off and placed in a ruled Syracuse dish (70 mm. diameter) to be counted under the binocular microscope. The counts of several dishes from the same suspension were found to differ only by 10 per cent of each other as a maximum, the majority being around 5 per cent. In the following determinations it was found desirable to count five dishes in each instance and to have the volume such that each dish contained between 100 and 200 renal corpuscles. An example may be given. The left kidney from a 9.9 kilo dog, after injection and maceration, was diluted to 6000 cc. Five 2 cc. portions gave the following counts; 161, 145, 156, 159, 149. The average is 154, which multiplied by 3000 gives 462,000 renal corpuscles in the entire kidney.

The accuracy of this method has been confirmed in several ways. The number of glomeruli in the kidney of the adult white rat has been carefully determined by Kittelson (1917), Arataki (1926) and Vimtrup (1928), and found to be about 30,000. The above method gave 29,750 and 31,750 in two adult rats. In a three-week-old rat 23,250 and 23,500 were found in the right and left kidneys, respectively, figures which agree well with those of Arataki (1926) for rats of the same age. Also, in the case of the rabbit, dog and cat our counts compare favorably with the careful ones of Nelson (1922) and Vimtrup

[4] If maceration is found to be insufficient after the kidney has been in distilled water for 24 hours, a second treatment with acid can be carried out.

(1928) on these animals. That an even suspension is obtained is shown by the agreement in the counting of separate samples. The renal corpuscles are not destroyed in the process in any significant number because repeated stirring or leaving the mixture for a day does not alter the count. However, in common with all injection methods a certain number of the glomeruli are uninjected. In this method, however, they are easily counted and were found to constitute from two to ten per cent of the total in various kidneys.

After this method was found successful, in addition to determining the number of glomeruli, it was thought desirable to measure their diameter for the purpose of making it serve as an index of the actual capillary surface in the renal corpuscles of the kidneys. In the literature there are few references to measurements of the renal corpuscles in the freshly teased kidney and many of their diameters in stained sections and in macerated specimens. Peter's (1907) measurements of the human renal corpuscle in fresh tissue show that it may either shrink or swell in maceration. It is well known that in fixed stained sections the tissue is greatly shrunken. Hence the reason for measuring fresh tissue is obvious and can be readily shown in the following examples where the mean of the greatest and least diameters of each of 10 renal corpuscles is used. All measurements in sections were made after fixing the kidney in Bouin's fluid, and making paraffin sections. In the case of the frog, measurements were made on living animals prepared for observing the kidney by reflected light.

The results on three frogs were as follows: (1) living 170μ, fresh 157μ, fixed stained sections 118μ; (2) living 158μ, fresh 161μ; (3) living 176μ, fresh 167μ.[5] In the dog (13.0 kilo), fresh tissue gave 163μ, unstained frozen sections 173μ, stained frozen sections 182μ, fixed stained sections 114μ, and injected macerated material 200μ. In the case of the pig, fresh tissue gave for the cortex 166μ, for the medulla 117μ, in the macerated material 191μ, in the fixed stained section 117μ. It was found that ox kidney in the fresh gave for the cortex 259μ, for the medulla 252μ, in the macerated specimen 267μ, and in fixed stained

[5] The renal corpuscles of the frog from teased fresh tissue were somewhat distorted from the shape as measured in the kidney of the living animal. Since the average of the two diameters does not differ markedly in the two cases, it has been used in expressing all measurements.

sections only 168μ. In the opossum they were found to be 176μ in the fresh, 134μ in the fixed stained material and finally in the ground hog 139μ in the fresh, and only 96μ in the fixed stained section.

From previous work it is well known that the number of glomeruli in each kidney of the same animal is approximately the same. In most of the following observations one kidney was used for counting, the other for measuring in the fresh. The observations on a series of 14

TABLE I

The number and size of the renal corpuscles in the dog

WEIGHT OF DOG	WEIGHT OF ONE KIDNEY	SURFACE AREA OF THE DOG	NUMBER OF GLOMERULI IN ONE KIDNEY	NUMBER OF GLOMERULI PER SQUARE METER OF BODY SURFACE (BOTH KIDNEYS)	NUMBER OF GLOMERULI PER GRAM OF KIDNEY	NUMBER OF GLOMERULI PER KILO OF BODY WEIGHT (BOTH KIDNEYS)	AVERAGE DIAMETER OF RENAL CORPUSCLE IN THE FRESH	AVERAGE DIAMETER IN MACERATION
kilos	*grams*	*sq. meters*					*micra*	*micra*
3.29		0.29	318,000	2,200,000		193,400	130	145
6.40		0.37	488,000	2,380,000		152,600	150	212
9.90	30.00	0.52	462,000	1,780,000	15,400	94,000	155	163
13.00	36.00	0.57	430,000	1,600,000	12,000	66,800	163	200
5.30	20.50	0.33	372,000	2,070,000	18,400	140,000	164	
6.45	25.50	0.40	414,000	1,980,000	16,500	130,000	167	
7.80	31.00	0.42	334,000	1,400,000	10,000	86,000	170	222
5.78	22.00	0.37	372,000	1,960,000	17,000	128,000	183	176
20.00	58.00	0.81	726,000	1,800,000	12,400	90,000	190	227
6.98	35.50	0.43	403,000	1,820,000	11,500	116,000	210	210
6.65	23.00	0.38	160,000	760,000	7,000	48,000	218	222
5.20		0.32	Rt. 378,000 Lt. 392,000	2,400,000		150,000		185
13.00		0.57	432,000	1,600,000		66,800		219
6.47 (6 months)		0.37	Rt. 573,000 Lt. 555,000	3,100,000		170,000		187

dogs are given in Table I. A large number of dogs were used because they vary widely in size and hence one can compare the relation of number of glomeruli and their size to the body weight, kidney weight and body surface. Several difficulties were encountered. First, in regard to surface area: the nutrition of the dogs varied greatly as did their general build, hence the formula of Cowgill and Drabkin (1927) was used in the last 6 dogs as a more accurate way of determining surface area instead of the formula of Meek (Lusk, 1928) based on

weight alone. Also, the age of the animals was not known. One dog obviously was only about 6 months of age, the others we assumed to be adults. These details cause wide variations in any figures expressing the above relationships. The only important observations one may draw from Table I is that the necessary glomerular capillary surface of different-sized dogs can be attained by both variation in size and in number of renal corpuscles per kidney.

In Table II are the observations on seven guinea-pigs, an animal of more stable size and nutrition. Here, as in the case of the rat, the number of renal corpuscles is practically constant but their size varies directly with the size (weight) of the animal.

TABLE II

The number and size of the renal corpuscles in the guinea-pig

WEIGHT	NUMBER OF GLOMERULI IN ONE KIDNEY	AVERAGE DIAMETER OF RENAL CORPUSCLES
grams		*micra*
174	75,700	94
175	78,000	100
206	74,900	103
331	70,250	109
428	75,500	114
467	78,300	122
565	75,700	126

In addition, a miscellaneous group of mammals was studied and the observations are tabulated in Table III. The glomeruli of the kidneys of the guinea-pig, monkey, opossum and ground-hog have not been counted previously. In the 3 last animals there are no constants for computing surface area which, however, was estimated by using the constants for the dog, pig and guinea-pig, respectively. In addition the values obtained in the case of the pig differ from those of Schweigger-Seidl (1865) and Putter (1911), who found 500,000 and 700,000 renal corpuscles per kidney, respectively. Putter also counted the ox kidney and found 4,500,000 and in the kidney of the mouse 27,000 glomeruli.

It is interesting that in this series 12 of the 17 animals should have the number of glomeruli per square meter of body surface within 20 per cent of 2,000,000 and that 11 of 13 adult dogs should have a simi-

TABLE III

The number and size of the renal corpuscles in various mammals

MAMMAL	BODY WEIGHT	WEIGHT OF ONE KIDNEY	SURFACE AREA	NUMBER OF GLOMERULI IN ONE KIDNEY	NUMBER OF GLOMERULI PER SQUARE METER BODY SURFACE (BOTH KIDNEYS)	NUMBER OF GLOMERULI PER GRAM OF KIDNEY	NUMBER OF GLOMERULI PER KILO OF BODY WEIGHT (BOTH KIDNEYS)	AVERAGE DIAMETER OF RENAL CORPUSCLES
	kilos	*grams*	*square meters*					*micra*
Macacus monkey no. 1	3.80	9.0	0.245	178,200	1,490,000	19,800	94,000	176
Macacus monkey no. 2	3.93	9.0	0.250	195,000	1,560,000	21,700	100,000	156
Opossum	2.00	5.2	0.140	91,200	1,300,000	17,500	91,200	175
Ground hog	1.21	1.8	0.093	96,000	2,060,000	53,000	160,000	139
Pig no. 1	43.30	75.5	1.26	1,248,000	2,000,000	16,000	54,000	162
Pig no. 2	50.00	78.0	1.27	1,138,000	1,800,000	14,400	45,400	170
Ox	410.00	640.0	5.70	3,992,000	1,500,000	6,220	19,580	255
Cat no. 1	3.50	25.5	0.22	214,500	1,940,000	9,000	120,000	150
Cat no. 2	2.75	8.0	0.19	184,000	1,940,000	23,000	156,000	133
Rabbit no. 1	1.90	6.5	0.20	Rt. 198,000 Lt. 199,400	2,000,000	33,000	198,000	
Rabbit no. 2	2.32		0.21	207,000	2,060,000		180,000	142
Rat no. 1	0.24	1.0	0.035	31,750	1,836,000	31,000	276,000	151
Rat no. 2	0.18	1.2	0.026	Rt. 29,750 Lt. 30,440	2,400,000	23,000	320,000	
Mouse no. 1	0.02	0.2	0.008	11,540	2,880,000	115,000	1,380,000	91
Mouse no. 2	0.022	0.2	0.009	10,150	2,440,000	110,000	1,150,000	109
Guinea-pig no. 2	0.565	1.9	0.058	75,700	2,600,000	37,500	268,000	126

lar number, although there is no constant relationship between the number per square meter and the size of the glomeruli. That there is no constant relationship between the number of corpuscles and the kidney weight or body weight is apparent.

CONCLUSIONS

1. A method that is relatively simple and accurate for the determination of the number of glomeruli in a kidney is described.

2. The measurement of the diameter of the glomerulus in teased fresh tissue is probably the most accurate method of determining its size.

3. For such animals as the rat, rabbit, pig, mouse, guinea-pig etc., which do not vary greatly in size in adult life, the number of glomeruli per kidney is fairly constant and the total glomerular surface is varied by change in the size of the glomerulus. In such animals as the dog, the number and size were found to vary in animals of different weights.

4. The number of glomeruli, their size and hence their total capillary surface seem to be more closely related to body surface than to any other measurement.

In conclusion, I wish to express my thanks to Dr. E. K. Marshall, Jr., for his encouragement and help in carrying out this work.

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AN EXPLANATION OF THE MECHANISM OF THE WASSERMANN AND PRECIPITATION TESTS FOR SYPHILIS[1,2]

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The purpose of this paper is to present an explanation of the mechanism of the complement fixation and precipitation tests used in the diagnosis of syphilis, based upon the underlying physico-chemical reactions involved. Ever since the discovery that an alcoholic extract of normal tissues could be used as "antigen" in the laboratory tests for syphilis, these reactions have been regarded as anomalous, and bearing only a superficial resemblance to such specific antigen-antibody reactions as the agglutination of bacteria or red cells by the homologous antiserum. However, as will be shown in the following pages, a causal analysis of these reactions does not support this view. Exactly the same factors are found to be involved in the precipitation of beef-heart lipoids by syphilitic serum (the Sachs-Georgi, Kahn, Meinicke, Müller, Hinton and other tests) as in the aggregation of bacteria, red cells or foreign protein by an antiserum. Similarly, the Wassermann reaction and the true Bordet-Gengou phenomenon (complement fixation by agglutinated bacteria) are completely analogous. The similarity is not merely superficial, as has been maintained, but extends to the basic physico-chemical processes involved.

The detailed protocols of the experiments on which these conclusions are based will appear in forthcoming papers:[3] the experimental data and the pertinent literature are briefly summarized in the following sections.

I. FLOCCULATION TESTS

When an antiserum is added to a bacterial or red-cell suspension, the antibody, (constantly associated with the globulin fraction of the

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[3] "Studies in Serology of Syphilis," Jour. Exp. Med. (In press.)

serum) is bound by the individual antigenic cells. The reaction takes place at their surface, the antibody being deposited as a thin film of protein, incompletely surrounding and demonstrable in the sensitized cells, chemically, immunologically and by a change in the surface properties towards those of serum globulin. The aggregation of these protein-covered bacteria or red cells is due to the fact that the antibody globulin loses its solubility in water by its combination, becoming as if coagulated ("denatured") on their surface. The sensitized cells, coated with this water-insoluble protein, now have the surface properties of solid particles of heat-coagulated globulin. They remain discrete only in the absence of electrolytes: as soon as a certain stabilizing surface charge is depressed by dilute NaCl, they cohere (agglutination; precipitation (1)).

Substituting *lipoid particles* for *bacteria*, and *syphilitic serum* for *antiserum*, the foregoing paragraph accurately describes the diagnostic flocculation tests for syphilis.

When an alcoholic extract of beef heart is diluted with saline, it forms a colloidally dispersed suspension in which minute refractile bodies (the active lipoids) can be seen by dark-field illumination. This suspension is very stable. The constituent particles behave as if they had more affinity for the surrounding water than for each other; for no cohesion is observed even in M/2 NaCl. Upon the addition of syphilitic serum, however, these particles aggregate even in NaCl N/15, forming the precipitate which constitutes the diagnostic criterion.

As in the case of true antibodies, the active substance in syphilitic serum causing this aggregation ("reagin") is always associated with the globulin fraction of the serum protein. Moreover, the washed precipitate, although consisting chiefly of the added lipoids, always contains some serum protein, demonstrable both chemically and by immunological experiments. The surface properties of these lipoid-reagin aggregates are no longer those of the original beef-heart lipoid, but even after washing until the supernatant fluid is nitrogen-free, can be shown to have changed in the direction of those of serum globulin.

Clearly, a specific substance in syphilitic serum, a reagin-globulin, has combined irreversibly with the particles of the antigen, forming an incomplete surface film of water-insoluble protein around each lipoid particle.

We are therefore no longer dealing with a stable colloidal lipoid suspension; the particles, covered with a mosaic of water-insoluble globulin, have the unstable properties of a suspension of heat-coagulated protein. Such particles have a marked tendency to cohere, which is prevented only by a surface charge due to the ionization of the protein (similarly charged particles repel each other). As soon as this stabilizing surface charge is depressed below a certain critical level, the particles can approach within their radius of attraction, and cohere to form sedimenting clumps.

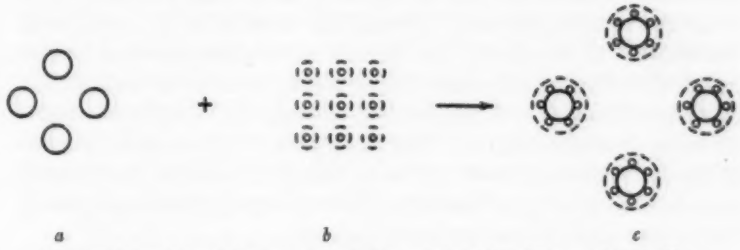
The protein-covered lipoid particles have a strong negative charge at serum pH (Na^+—globulinate$^-$). In the absence of electrolytes no aggregation is observed, because this surface charge suffices to keep the particles apart (mutual electrostatic repulsion). The ion which permits aggregation by suppressing this negative surface potential should be the one with opposite charge, the cation. And it is actually found that with both NaCl and Na_2SO_4 a concentration of N/15 to N/20 is necessary to produce flocculation (i.e., valence of anion makes no difference); while with $BaCl_2$, as little as M/400 suffices, proving that it is the cation which determines the flocculation of the reagin-covered antigen particles, a cohesion primarily of the protein surface, and only incidentally of the underlying, inert lipoid.

It should be pointed out that, as in the case of bacteria, protein is adsorbed by these lipoid particles even from normal serum, as shown by the change in their surface properties (movement in an electrical field; isoelectric point, etc.). Unlike syphilitic reagin-globulin, however, this normal protein is unchanged during adsorption. It remains water-soluble, can be readily removed by washing, and for these reasons does not facilitate agglutination. The difference between normal and syphilitic protein after adsorption by the antigen particles is analogous to the difference between a solution of globulin, stable even in 2 M NaCl, and an unstable suspension of the same protein after coagulation by heat, when the constituent particles are readily agglutinated by as little N/20 NaCl. The different properties of the lipoid suspension in normal and syphilitic serum are due simply to the different physical states of the protein with which it has combined.

One can only hypothecate as to the cause for the pseudo-coagulation of all antibodies, including syphilitic reagin-globulin, when they

combine with their specific antigen. A tentative theory has been suggested elsewhere (1).

The mechanism involved by the flocculation of beef heart lipoids by syphilitic serum may be summarized in the following diagram.

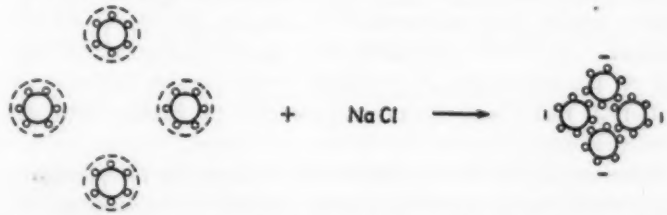


a *b* *c*

A. Lipoid particles of the antigen: stable, not flocculated by < N/1 NaCl.

B. Reagin globulin of syphilitic serum.

C. Lipoid-reagin complex, with surface properties determined by an ionizing film of water-insoluble (denatured) reagin-protein. No aggregation because of mutually repelling surface charge.



D. Discharge, permitting cohesion of the particles: a "cohesion primarily of the reagin-protein surface, and only incidentally of the underlying, *inert* lipoid."

FIG. 1

II. WASSERMANN REACTION

Many attempts have been made to explain the fact that when beef-heart (or liver) lipoids are mixed with syphilitic serum in the presence of fresh serum, a thermolabile hemolytic component of the latter, complement, is destroyed (complement-fixation; Bordet-Wassermann test). Enzymes, aggregation, vague "colloidal phenomena" have all been invoked to explain an apparently non-specific and anomalous reaction.

It has already been shown (2) that specific complement fixation by agglutinated bacteria (Bordet-Gengou phenomenon) is an irreversible adsorption of complement by the same film of antibody-globulin which causes their aggregation. In keeping with this explanation, sensitized red cells also absorb complement, for they also are covered with this antibody-protein: indeed, this adsorption is an essential preliminary to hemolysis (3). Specific complement fixation in general is therefore not the *result* of aggregation, but concomitant with it. Complement-fixing and aggregating antibody are identical. Agglutination (precipitation) and the ability to adsorb complement are different manifestations of the same change induced in the bacterial or red-cell surface by the specific antiserum, namely, the deposition of a film of physically altered antibody-globulin.

The fundamental similarity just established between the "specific" agglutination of bacteria or red cells by an antiserum and the flocculation of beef-heart lipoids by syphilitic serum suggests a simple explanation for the Wassermann reaction. As in the case of the specific Bordet-Gengou phenomenon, the same film of reagin-globulin around the lipoid particles that causes their flocculation would also adsorb complement. To prove this thesis one needs only establish the identity of the substances in syphilitic serum causing flocculation (Sachs-Georgi, Kahn, and others) and complement fixation (Bordet-Wassermann test).

The following is a brief summary of the evidence for this identity. (1) Complement-fixing, like flocculating, reagin is always associated with the globulin fraction of serum protein. (2) Every Wassermann test causes a submicroscopic aggregation of the lipoid particles, not visible macroscopically because of their dilution. (3) Conversely, the precipitate obtained in a positive Kahn test fixes complement powerfully. (4) Precipitation tests remove both the precipitating and complement-fixing substances from syphilitic serum. (5) The lipoids in the precipitate are no longer able to react with syphilitic serum in the Wassermann test, *i.e.*, saturating them with precipitating reagin has also saturated them with complement-fixing reagin. But when this precipitate is heated to 100°C. for a few seconds, which destroys the protein film responsible for flocculation, the antigen particles

regain their ability to give complement fixation with a positive serum. Clearly, the same globulin film constitutes both the flocculating and complement-fixing agency. Normal serum protein, although it is absorbed, does not attach to the active groups of the lipoid particles, and therefore does not preclude their use in a Wassermann reaction. (6) Finally, if one measures quantitatively the amounts of reagin in a group of sera by both types of test, it is found that the titres always run parallel: a serum containing three and one-half times as much reagin as tested by the Wassermann reaction contains just three and one-half times as much reagin as tested by, *e.g.*, the Kahn reaction. ***Complement fixation in the Wassermann reaction is due to the same film of reagin-globulin which causes flocculation.***

TABLE I

Optimum conditions for Wassermann and flocculation tests

	pH	ELECTROLYTE CONCENTRATION	BIVALENT IONS	SHAKING	TEMPERATURE	VOLUME DECREASE
Wassermann	5.8 to 8.3	N/15 to N/4	Complete inhibition	No effect	< 40°	No effect
Flocculation.....	Any reaction, optimum at 3.5 to 6.0	N/15 to N/1	Acceleration	Acceleration	< 60°	Enormous acceleration

The almost complete correspondence between the two types of test is simply confirmatory. The fact that certain changes in the conditions under which they are carried out will increase the sensitivity of the one type of reaction, and suppress the other, does not, of course, prove that two different substances are involved. Both reactions are due to the same factor: a film of reagin-globulin around the lipoid particles. Their *subsequent* aggregation or their *subsequent* adsorption of complement are entirely different physico-chemical phenomena, with quite different optimal conditions, listed below.

From the table it is seen that, although both are obtained at serum tonicity, pH 7.4, and at 37°C., almost any change in conditions will affect the two tests differently; not because there are two different reagins, but because we are dealing with two different manifestations of the same substance.

SUMMARY AND DISCUSSION

There is not merely a superficial similarity between the flocculation tests for syphilis and bacterial agglutination by an antiserum, or between the Bordet-Gengou phenomenon (specific complement fixation) and the Wassermann test. The analogy extends to the basic mechanism of the reactions.

Reagin, an altered globulin in syphilitic serum, combines with the colloidal particles of beef-heart lipoid ("antigen"). The surface film of protein thus formed sensitizes the particles to flocculation by electrolyte (Sachs-Georgi, Kahn, and others), and also adsorbs complement (Wassermann). Antibody-globulin affects bacteria, red cells or foreign protein in exactly the same manner.

The serum change characteristic of syphilis may therefore well represent an antibody response to products of infection. As will be shown, the fact that normal-tissue lipoids can be used instead of spirochetes as the antigen in the test-tube reaction does not exclude this possibility.

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THE EFFECT OF POTASSIUM IODIDE ON THE PULSE RATES OF NORMAL INDIVIDUALS[1]

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There appears to be no settled opinion concerning the effect of iodine on the pulse rate of normal individuals. Cushny (1) states that no change in the heart, pulse or blood-pressure could be observed even after prolonged treatment with iodides. Nevertheless, in certain Clinics the term "iodine tachycardia" is used to describe the elevated pulse rate occasionally seen in patients under treatment with iodides. There is some evidence to support this view. The statement has also been made that a fall in pulse rate occurs.

Gurewitsch (2), in Basel, studied a series of patients under treatment with potassium iodide and found an increased pulse rate (10 to 50 per minute) in 68 per cent. The tachycardia disappeared in a few days after withdrawal of the drug. Bloom (3), in reporting somewhat similar material from Berne, noted an increase (3 to 33 per minute) in 75 per cent of 23 cases. The majority of the latter subjects had tuberculosis or syphilis which might be considered a modifying factor. Goiter and "Iodine Basedow's" are common in both localities. Stockman and Charteris (4) found no change in the pulse rates of patients treated with sodium iodide and potassium iodide in doses varying from 1 to 20 grams daily. The best study has been made by Read, Walker and McKenney (5) on 12 normal individuals who were placed on 10 drops of Lugol's solution daily for ten days. There was a slight increase in 7, no change in 3 and a slight decrease in 2 cases. The *means* showed an inconsequential increase.

In a study of the effect of iodine on the electrocardiogram in a series of normal individuals (6) it was found that 8 out of 10 exhibited an increased heart rate after ingestion of potassium iodide and that the means of the series showed a progressive increase during the period of exhibition of the drug. The observations were too few, however, to

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analyze statistically. A review was therefore made of the records of patients who had been treated with iodides over considerable periods of time in the wards of the Johns Hopkins Hospital. Cases of thyroid disease, syphilis, tuberculosis, myocardial insufficiency or of fever due to any cause were rigidly excluded. No patients were accepted who had received other drugs, such as atropine or digitalis, which might have affected the pulse rate. The majority were cases of arteriosclerosis, neuritis and arthritis. The average of seven successive morning pulse rates was taken before administration of the drug and the same for the seven days prior to its discontinuance. When administration of the drug covered sufficient time, the average of each week's morning pulse rates was also noted. The usual dose of potassium iodide was 2.0 grams daily and the duration of its exhibition varied from 8 to 140 days. The youngest patient was 2 years of age and the oldest 80. Potassium iodide was the drug used in all patients.

RESULTS

The mean of the 34 control pulse figures is found to be 82.6 and that of the iodine pulse figures 87.5, giving a difference in the means of +4.9. The probable error of this difference is ±2.1. It is assumed that a difference, in order to be of significance, must have a ratio, when compared with its probable error, of 3 to 1 or greater. For these figures the ratio is but 2.3 to 1 and the difference cannot therefore be considered as significant. Read, Walker and McKenney (5) treated their figures similarly. Such statistical treatment is based, however, upon the assumption that all individuals in the series react in like manner to the drug, an assumption which the following data show to be incorrect.

Table I shows the data obtained in this study. Each pulse figure represents the average of 7 or more observations. The standard deviation and the probable error of the mean have been calculated for each of these series of variants and the probable error of each difference is included in the table. It will be noted that an apparent increase has occurred in 24 instances, an apparent decrease in 9, and no change in one. When the ratio of each difference to its probable error is calculated, however, it is seen that there is a significant increase in 12 instances, a significant decrease in 5 and no change in 17. In other

TABLE I

Effect of potassium iodide on normal pulse rate

MED. NO.	AGE	DAYS ON KI	TOTAL GRAMS TAKEN	CONTROL PULSE	PULSE DURING IODINE	PULSE DIFFERENCE	PROBABLE ERROR OF DIFFERENCE	RATIO OF DIFFERENCE TO P.E. OF D.	SIGNIFICANT PULSE CHANGE*
3620	45	21	42	75.4	77.1	1.7	3.3	0.5	0
3637	56	27	54	84.0	74.5	9.5	1.4	6.8	−
3640	66	34	68	78.2	96.5	18.3	2.6	7.0	+
3652	42	77	733	64.2	92.0	27.8	2.0	13.9	+
3656	68	13	26	79.4	76.5	2.9	1.9	0.6	0
3671	49	10	20	78.2	58.9	19.3	1.3	14.8	−
3677	38	18	36	81.4	84.5	3.1	2.3	1.3	0
3697	65	12	26	72.0	83.4	11.4	3.1	3.7	+
3721	42	140	280	97.0	110.0	13.0	2.3	5.7	+
3746	33	40	80	72.8	88.5	15.7	2.3	6.8	+
3750	46	61	124	94.2	82.5	11.7	2.3	5.1	−
3859	68	30	60	76.6	79.4	2.8	2.3	1.2	0
3873	56	74	148	75.7	75.7	0	2.8	0.0	0
3878	24	50	253	114.2	101.7	12.5	3.1	4.0	−
3883	66	12	36	85.6	98.5	12.9	2.9	4.5	+
3961	80	16	48	66.6	65.4	1.2	2.1	0.6	0
4047	28	10	30	91.1	91.7	0.6	1.7	0.3	0
4102	80	29	58	95.8	97.8	2.0	4.2	0.5	0
4201	36	8	28	82.8	90.4	7.6	2.8	2.7	0
4320	53	120	240	65.3	82.2	16.9	2.2	7.7	+
10794	38	16	32	70.4	80.2	9.8	4.5	2.2	0
10817	63	20	40	79.4	87.4	8.0	1.8	4.4	+
10820	46	14	20	77.4	84.0	6.6	2.3	2.9	0
10910	61	16	32	77.0	78.2	1.2	3.5	0.3	0
11025	38	30	75	98.3	90.5	7.8	2.0	3.9	−
11028	38	8	37	63.7	89.7	26.0	2.5	10.4	+
11033	47	9	18	85.7	89.1	3.4	2.9	1.2	0
16643	66	15	30	95.5	102.0	6.5	3.3	2.0	0
16648	30	23	182	83.1	79.7	3.4	1.9	1.8	0
16657	44	33	66	97.6	94.2	3.4	1.8	1.9	0
16770	3	35	11	124.8	127.8	3.7	2.5	1.5	0
16898	44	34	105	73.0	86.3	13.3	2.3	5.8	+
16963	34	30	90	80.5	88.0	7.5	2.0	3.7	+
17040	14	25	25	73.2	94.3	21.1	3.8	5.5	+

* A change is only considered to be significant when the ratio of the difference to the probable error of that difference is 3:1 or greater.

words 35.0 per cent of the 34 cases exhibit an increase pulse rate under iodine, 15.0 per cent a decrease and the remainder no real change. These changes vary from 8 to 28 beats per minute.

Figure 1 illustrates graphically the changes that occurred in cases No. 4320 and No. 11028 of this series following the administration of iodine. In the latter the effect of its discontinuance is also shown.

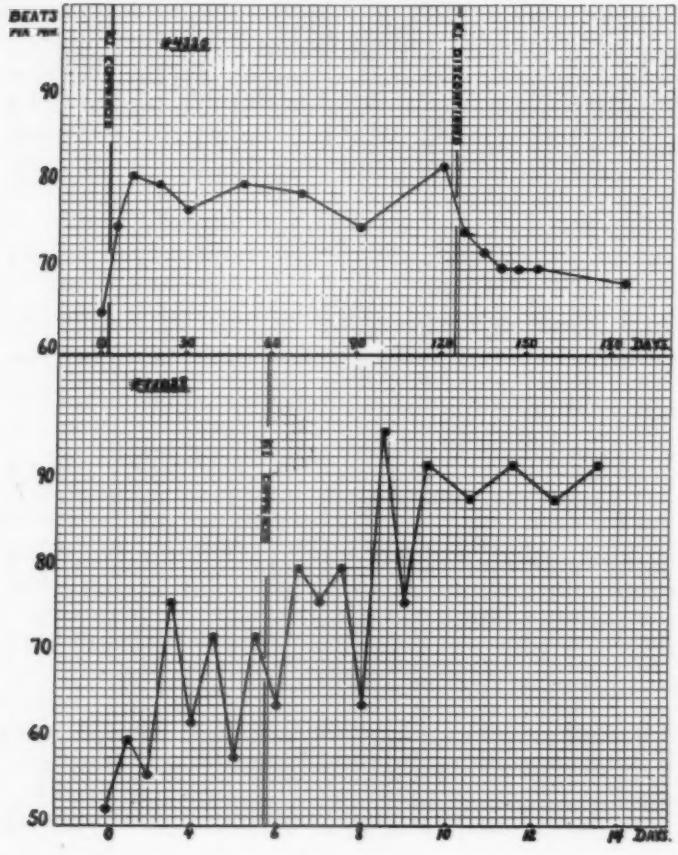

FIG. 1

The upper curve represents a case studied over some 180 days, each point being the average of 7 consecutive daily pulse rates. The rapid elevation of rate, its persistence during iodine therapy and its dis-

appearance after removal of the drug are well shown. The lower curve represents a case followed for 12 days, each point being a separate pulse rate observation. The increase is seen to occur about the third day after the iodine was begun. In all of the cases exhibiting significant alterations in pulse rate, the change occurred gradually at about the third to the seventh day and reached a maximum about the tenth. Upon discontinuance of the drug, the pulse fell to normal within a week or so.

SUMMARY

A statistical analysis was made of the pulse rates of 34 patients, without thyroid disease or other interfering circumstances, to whom potassium iodide had been administered. Following administration of the drug, 12 showed a significant increase in pulse rate and 5 a significant decrease. These changes came on gradually about the third to the seventh day and reached a maximum at about the tenth day. The rate returned to normal within a week or so after the drug was discontinued.

I am indebted to Miss Rebecca Marshall for assistance with the case-records and calculations.

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THE EFFECT OF THE INGESTION OF POTASSIUM IODIDE ON THE ELECTROCARDIOGRAM OF NORMAL INDIVIDUALS[1]

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It has been reported by several observers that changes occur in the electrocardiograms of patients with hyperthyroidism following iodine therapy or thyroidectomy. Krumbhaar (1) studied 51 patients with goitre, the majority with hyperthyroidism, and noted unusually high T-waves in the majority of instances. Following operation these returned to normal in half the cases. These records, however, were taken with an Edelmann galvanometer and the string deviations were therefore not standardized. Hamburger and others (3) noted the very high T waves in hyperthyroidism and showed that iodine therapy produced a fall in their amplitude which paralleled the fall in basal metabolic rate. Following thyroidectomy, these changes were even more striking—in three cases proceeding to inversion. The low T waves and QRS complexes found in cretinism and myxedema are well recognized (2, 4, 5, 6, 7, 8). They increase in amplitude upon thyroid administration, the increase paralleling the rise in basal metabolic rate. White and Aub (2) concluded that there was little relationship between the basal metabolic rate and the voltage of the end phase. However, a study of their protocols shows that of 12 cases in which comparison is possible, a parallelism exists between the height of the T waves and the basal metabolic rate in 8 instances.

It seemed of interest, therefore, to determine whether the galvanometric records of normal individuals exhibited changes when iodine was administered in therapeutic doses. Hamburger, and others, (9) attempted to answer this question, but obtained conflicting results. Some writers have claimed on slender evidence, that iodides, in therapeutic doses, exert an injurious influence on the cardiovascular system.

[1] Submitted for publication September 20, 1930.

METHOD

Iodine, in the form of Potassium Iodide, was administered by mouth to fourteen normal members of the hospital staff each day in doses of 1.0 gram per day during the first week, 2.0 grams per day during the second week and 3.0 grams per day during the third week. Four of the subjects were forced to drop out because of rather severe iodide reactions. The remaining ten took the drug for periods ranging up to 22 days. Lugol's solution was used for the first few days but gave way to Potassium Iodide owing to bitter complaints of the recipients. In this connection it is suggested that enthusiasts for large doses of Lugol's solution try a short course of the drug themselves.

Electrocardiographic records were made before administration of the drug and every five days thereafter till the end of the experiment. They were taken with standard Einthoven leads on a Hindle galvanometer in use for routine purposes. The subjects were made to rest in the sitting posture for ten minutes before records were made and the heart rates were subsequently read in the third lead thus allowing a further short period of rest. Skin resistance was measured in every instance and if above 2000 ohms the electrodes were removed, the skin rubbed with alcohol and remoistened with saline before the written records were made. This procedure effectively brought the resistance below 2000 ohms in every case. The string was standardized in the usual manner to give a deflection of 1.0 cm. with 1.0 millivolt. Records were taken between 4 and 5 P.M. in order to rule out the possible effect of food on the cardiac rate and the written curves.

DISCUSSION

Table I is a tabulation of the data from each individual before the drug was commenced and at the completion of the course of potassium iodide. The intervening records were examined but showed no significant changes. Measurements were also made of the other deflections in the electrocardiogram, but they showed no alteration and are not included. It is apparent that no change of any consequence occurred as a result of the ingestion of potassium iodide. The T-wave changes said to occur after iodine therapy in patients with hyperthyroidism do not occur in this series of normal individuals. In Lead I slight

TABLE I

	SUBJECT 1		SUBJECT 2		SUBJECT 3		SUBJECT 4		SUBJECT 5		SUBJECT 6		SUBJECT 7		SUBJECT 8		SUBJECT 9		SUBJECT 10	
	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine	Before iodine	After iodine
Number of days on KI	5		15		19		16		15		21		20		22		20		19	
Total KI taken (gms.)	9		21		22		23		25		37		40		41		42		45	
Skin resistance (ohms)	1400–1400		1300–2000		1200–1400		1000–1700		400–1000		1400–1900		1000–1300		–2000		2000–1400		1100–1400	
B. M. R	−14	−9	−14		−13	−19	−20	−29	−12	−2	−16	−9	−19	−19	−13	−12	−4	−3	−28	−37
P-R interval (secs.)	0.20	0.20	0.16	0.17	0.16	0.17	0.15	0.15	0.19	0.20	0.19	0.17	0.18	0.18	0.14	0.14	0.17	0.17	0.19	0.19
R-T interval (secs.)	0.24	0.23	0.26	0.28	0.24	0.24	0.23	0.23	0.21	0.21	0.25	0.23	0.26	0.24	0.22	0.21	0.24	0.19	0.22	0.20
QRS duration (secs.)	0.04	0.06	0.08	0.08	0.06	0.06	0.03	0.03	0.04	0.03	0.06	0.05	0.05	0.06	0.04	0.05	0.05	0.05	0.05	0.05
T duration (secs.)	0.18	0.17	0.21	0.19	0.20	0.19	0.20	0.18	0.18	0.19	0.12	0.13	0.21	0.21	0.20	0.18	0.16	0.13	0.20	0.15
T I—height (mms.)	5.0	3.5	5.0	4.5	2.5	2.5	2.5	2.0	3.5	3.0	2.0	2.0	2.5	4.0	1.5	1.5	3.0	2.0	2.5	2.0
T II—height (mms.)	4.0	3.0	5.0	5.5	4.0	4.0	3.5	2.5	3.0	3.0	1.5	1.5	6.5	6.5	5.0	4.0	4.0	2.0	4.5	4.0
T III—height (mms.)	0*	2.0	2.0	0.5*	1.5	2.0	1.0	1.0	1.0	1.5	1.0	0*	3.5	3.0	4.0	2.0	2.0	0.5	4.0	3.0
Heart rate	71	75	68	57	75	79	67	79	83	88	69	75	60	69	59	82	68	63	72	91

* Biphasic.

diminution in amplitude occurred in six instances and slight increase in two, neither being outside the usual limits of variation. Inversion was not seen, although T III became biphasic in two instances. The skin resistance and the basal metabolic rate showed no alterations that could be attributed to the iodine. The effect on the heart rate is discussed elsewhere (10).

It would appear therefore that the electrocardiographic changes wrought by iodine in hyperthyroidism may be the result of its general effect upon the disease and not of any specific action of the drug on the cardiovascular system.

CONCLUSIONS

Potassium Iodide in therapeutic doses has no significant effect upon the electrocardiogram of normal individuals.

We are indebted to Miss J. A. Vickers and to Mr. Wm. M. O'Brien for technical assistance in this study.

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